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## Original Communications

### THE ETIOLOGY OF ACUTE INFECTIOUS GINGIVOSTOMATITIS (VINCENT'S STOMATITIS)


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THE purpose of this report is to present clinical and experimental evidence to prove that the herpes simplex virus is the primary etiologic agent of that common disease of early childhood which in a previous publication I have designated by the descriptive term "acute infectious gingivostomatitis,"[1] a disorder variously known as Vincent's stomatitis, Vincent's angina, ulcerative or ulceromembranous stomatitis, fusospirochetal stomatitis, trench mouth, etc.

My studies have been stimulated primarily by a dissatisfaction with prevailing theories of etiology, particularly with the fusospirochetal theory, and more specifically by the following reports:

Youmans,[2] in 1932, reported recovery of the herpes virus for the first time from what was apparently an instance of this disease of childhood occurring in a woman 24 years of age. There are, to be sure, earlier reports in the German literature associating certain oral inflammations with the presence of the herpes simplex virus.[3, 4, 5] However, one cannot be certain that the reported cases were instances of acute infectious gingivostomatitis.

Two of the three cases reported by Long,[6] in 1933, were probably instances of acute infectious gingivostomatitis occurring in adults. In the oral lesions of one of these two, the herpes virus was present.

In 1938, Dodd, Johnson, and Buddingh[7] reported twelve cases of what were unquestionable instances of acute infectious gingivostomatitis in children, in which rabbit corneal inoculations of material from the mouth lesions were invariably followed by the development of histologically verified herpetic keratoconjunctivitis.

Burnet and Lush[8] in 1939 cited two cases of what they termed "aphthous stomatitis" in young children. The herpes simplex virus was found in the mouth lesions, and the blood serum "contained no significant antibody" against the herpes virus. Three weeks later the blood serum "showed definite antibody." It is impossible to determine

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from the incomplete clinical description whether or not these were cases of acute infectious gingivostomatitis.

These observations, the only ones of their kind in the literature,* may be accepted as proof that the virus of herpes simplex is present with a high degree of regularity in the lesions of acute infectious gingivostomatitis. This important finding certainly provides a promising etiologic hypothesis but is scarcely sufficient evidence to establish proof that the virus of herpes simplex is the cause of this disease.

## FILTERABLE VIRUSES AND ETIOLOGY

Filterable viruses cannot be dealt with exactly as are bacteria in establishing an etiologic relationship to a specific disease. Nevertheless, the spirit of Koch's postulates[9] still guides us. Rivers[10] in a discussion of viruses and Koch's postulates states, "(a) A specific virus must be found associated with a disease with a degree of regularity. (b) The virus must be shown to occur in the sick individual not as an incidental or accidental finding but as the cause of the disease under investigation." In dealing with an ubiquitous agent, such as the virus of herpes simplex, evidence of an etiologic relationship to the disease in question should be viewed critically lest we be misled in the same manner as the proponents of the fusospirochetal theory have been in the past.

## CLINICAL MATERIAL

The 45 case studies which form the basis of this report were all observed in San Diego during the seventeen months from August, 1938, to January, 1940. There were 23 consecutive personally observed cases of acute infectious gingivostomatitis and 22 control cases, 13 of which manifested oral inflammations not characteristic of acute infectious gingivostomatitis, whereas 9 were normal healthy children. One of the latter group was a healthy volunteer for oral inoculation with the virus of herpes simplex.

The past history of the child was obtained with special reference to diet, antecedent illness, previous soreness of the mouth and exposure to anyone with a sore mouth or "cold sore." The history of the present illness was elaborated with care as to the time and nature of the first symptom and the daily course of events up to the time of the first examination. Each child was completely examined, the temperature recorded, whenever possible a sterile specimen of blood obtained, material taken from the oral lesions for dark-field examination and stained smear and for immediate inoculations onto the scarified cornea of a young female white rabbit. The child was observed at intervals of a few days until well. After an interval of a few weeks another sterile blood specimen was obtained and the mouth inspected. The gross data on the cases of acute infectious gingivostomatitis are given in Table I and for the control cases presenting other types of oral inflammation in Table II.

## EXPERIMENTAL METHODS

*Rabbit Inoculations.*—The rabbits used in this study were all white females, mostly young animals of approximately 1,500 Gm. in weight. There was no illness among

*After the present study was completed and reported at the Region IV Meeting of the Academy of Pediatrics in San Francisco, 1941, and after the manuscript had been approved for publication by THE JOURNAL OF PEDIATRICS, a study of the same subject with practically the same findings appeared in the Journal of the American Medical Association (Scott, McN.: J. A. M. A. 117: 999, 1941.)

the animals except that induced by the inoculations. The stock animals were hutched several miles away, whereas the test animals were kept in separate outdoor hutches near the laboratory. Only one instance of possible accidental cross infection with the virus occurred. Experiments with other viruses were not in progress in this laboratory during the course of this study.

In making the corneal inoculations the rabbit was anesthetized with sodium pentobarbital administered intravenously. Several deep scratches were made in the cornea with a cystotome. Material from the child's mouth was obtained by scraping the lesions with a small dull ring curette. This material was immediately rubbed gently into the corneal lacerations. In no case did more than fifteen or twenty seconds elapse between the time the material was obtained and its inoculation into the rabbit's eye.

*Dark-field Examination and Stained Smear.*—Material for dark-field preparations was obtained from the gingivodental sulcus with the blunt end of a wooden applicator. Smear material was obtained in the same manner, fixed with heat and stained with steaming 5 per cent methylrosaniline (gentian violet).

*Virus Isolation.*—The material obtained from the children's mouths and inoculated into the rabbits' eyes was a mixture of tissue cells, pus cells, bacteria, oral anaerobic organisms, fungi, mucus, saliva, debris, and the virus of herpes simplex.

Success in isolating several strains of the virus was accomplished in the following manner. It was noted, as Londsteiner[11] and Fessler and Feyrter[5] had previously noted in studies of the Aphthoid of Pospischill, that careful routine stained smear and dark-field examinations of the pus from the rabbit's eye often revealed no visible bacteria. The pus in several cases was aspirated with a sterile pipette, suspended in a small amount of saline, cultured and inoculated intracerebrally into rabbits and mice. Cultures* of the pus were in these cases sterile, and the animals after the usual incubation period developed symptoms of herpetic encephalitis and died. The brains, removed with sterile precautions, were found to be sterile on culture but when ground and inoculated into rabbits or mice produced characteristic lesions in the brains or eyes, depending upon the site inoculated. Repeated serial transfers of the infection from animal to animal were easily accomplished. The eye lesions so produced contained acidophilic intranuclear inclusions. The sterile virus-containing material was innocuous for convalescent herpes immune rabbits and convalescent children.

*Intracranial Inoculations.*—Intracranial inoculations into rabbits were performed by puncturing the skull through a palpable groove in the bone just behind the eye. Not more than 0.25 c.c. of material was injected at one time.

Intracranial injections into mice were performed under ether anesthesia through the top of the head a little to one side of the midline directly into one of the cerebral hemispheres. The routine volume injected was 0.03 c.c. Mice so injected invariably run about, feed, and behave quite normally as soon as the effects of the anesthetic have worn off.

*Virus Neutralization Tests.*—Blood was obtained from the children and permitted to clot. The serum was drawn off with a sterile pipette and transferred to another sterile test tube. In most cases it was not convenient to test each sample of serum as it was obtained. In order to facilitate storage without loss of immune substances, several 0.50 c.c. samples of each serum specimen in which storage for more than a few days was necessary were frozen and dried in vacuum and stored in the refrigerator until tested.

At the time of testing the lyophile serum was reconstituted by the addition of sufficient distilled water to restore the original volume. An equal volume of 10 per cent sand-ground normal saline emulsion of herpes simplex virus containing

*All cultures were made in dextrose tryptosephosphate broth.

TABLE

CASES OF ACUTE INFECTIOUS

| NAME OF PATIENT | NUMBER | AGE (YEARS) | SEX | MONTH | EXPOSURE | | SIGNS AND SYMPTOMS | | | | | DURATION (DAYS) | DARK-FIELD EXAMINATION | | | | SMEAR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | COLD SORE | SORE MOUTH | TEMPERATURE | GINGIVITIS | ULCERS | ADENITIS | FETOR | | TREPONEMAS | FUSIFORM BACILLI | VIBRIAS | SPIRILLA | |
| L. B. | 1 | 1 1/6 | F. | 3 | 0 | 0 | 100.4 | + | + | + | + | 16 | + | + | + | + | |
| B. B. | 2 | 2 2/3 | F. | 9 | | 0 | 103 | + | + | + | 0 | 15 | + | + | + | + | |
| G. C. | 3 | 1 | M. | 5 | 0 | + | 101 | + | + | + | + | 10 | + | + | + | + | |
| J. C. | 4 | 2 | M. | 5 | 0 | 0 | 104 | + | + | + | + | 12 | + | + | 0 | 0 | + |
| M. C. | 5 | 8 | F. | 7 | + | 0 | 99.2 | + | + | + | + | 12? | + | + | + | 0 | |
| W. F. | 6 | 2 1/2 | M. | 2 | 0 | 0 | 103 | + | + | + | + | 10? | + | + | + | + | |
| D. G. | 7 | 15 | F. | 9 | + | 0 | 101.4 | + | + | 0 | + | 15 | | | | | |
| S. G. | 8 | 1 1/6 | M. | 9 | | 0 | 102 | + | + | 6 | 0 | 12 | 0 | + | + | 0 | |
| M. H. | 9 | 9 1/3 | F. | 6 | + | 0 | + | + | + | + | + | 13 | + | + | + | + | + |
| G. M. | 10 | 2 | M. | 9 | + | 0 | + | + | 0 | + | + | 14 | | | | | |
| C. M. | 11 | 2 3/4 | F. | 1 | 0 | 0 | 103.6 | + | + | + | + | 12 | + | + | + | + | |
| G. O. | 12 | 1 1/2 | F. | 10 | 0 | 0 | 102 | + | + | | | | | | | | |
| C. O. P. | 13 | 4 | M. | 9 | 0 | + | 103.5 | + | + | + | + | | | | | | |
| M. P. | 14 | 1 1/2 | M. | 11 | 0 | 0 | 103 | + | + | + | + | 12 | + | + | + | + | |
| C. P. | 15 | 4 | M. | 5 | + | 0 | + | + | + | + | + | | + | + | + | + | + |
| M. S. | 16 | 1 1/2 | F. | 7 | + | 0 | ? | + | 0 | + | + | 16 | + | + | + | 0 | + |
| R. V. | 17 | 1 1/2 | M. | 7 | 0 | 0 | 103 | + | + | + | + | 15 | + | + | + | 0 | + |
| M. V. | 18 | 6 | F. | 7 | + | 0 | 101.6 | + | + | + | + | | + | + | + | 0 | + |
| T. W. | 19 | 3 1/2 | F. | 9 | 0 | 0 | 103.6 | + | + | 0 | + | | | | | | |
| J. S. | 20 | 1 3/4 | F. | 10 | 0 | 0 | 102+ | + | + | 0 | + | 13 | | | | | |
| J. C. | 21 | 1 1/4 | F. | 12 | 0 | 0 | 102 | | | + | + | | | | | | |

*Positive (+) result indicates animal not immune. Negative (–) result indicates animal immune.

| RABBIT CORNEAL INOCULATION | | | | | SERUM NEUTRALIZATION TESTS | | | | CONVALESCENT CASE IMMUNITY | | | COMMENTS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PRIMARY | | SUBSEQUENT IMMUNITY | | | | | | | | | | |
| DAY OF DISEASE | RESULT | TIME (MO.) | VIRUS | RESULT* | DAY | RESULT | DAY | RESULT | TIME (MO.) | VIRUS | RESULT | |
| 5 | + | 3<br>3 | C. P.<br>H. F. | -<br>- | 5 | - | 31<br>75 | +<br>+ | 2 | C. P. | - | Rabbit corneal inoculation negative at thirty-one days and dark-field examination same as on fifth day |
| 5 | + | 7<br>8<br>9<br>10 | L. B.<br>H. F.<br>C. P.<br>H. F. | -<br>±<br>-<br>- | | | | | | | | Rabbit corneal inoculation negative at nine months and dark-field examination same as on fifth day |
| 2 | + | 1½<br>3 | C. P.<br>H. F. | -<br>- | 2 | - | 33 | + | 1 | C. P. | - | Rabbit corneal inoculation negative at thirty-seven days and dark-field examination showed only a few F.B. |
| 4 | + | 1 | H. F. | - | 5 | ± | 12<br>39 | +<br>± | 1½ | C. P. | - | Rabbit corneal inoculation negative at forty-eight days and dark-field examination revealed even more anaerobes |
| | | | | | 7 | - | 35 | + | | | | Original rabbit inoculated was subsequently found to be immune to herpes virus |
| 7 | +? | 3<br>5 | C. P.<br>H. F. | -<br>- | | | | | | | | Original rabbit had a delayed but typical reaction in eye; on eighth day after inoculation failed in serial transfer |
| 11 | - | | | | 4 | + | | | | | | Child admits promiscuous chewing of other people's gum |
| 3 | + | 7<br>8<br>8½ | L. B.<br>H. F.<br>C.P. | -<br>-<br>- | | | | | | | | Two serial transfers positive; animals immune to H. F., C. P., and L. B. |
| 6 | - | | R. V.<br>H. F. | +<br>- | 6 | + | 35 | + | | | | |
| 12 | - | 4½ | H. F. | + | | | | | | | | Case first seen when nearly well |
| 3 | + | 3½<br>4<br>4½ | L. B.<br>H. F.<br>C. P. | -<br>-<br>- | 3 | - | 35<br>150 | +<br>± | | | | Mouth free of herpes virus at 5 months |
| 5 | + | 7<br>7½<br>8 | L. B.<br>H. F.<br>C. P. | -<br>-<br>- | | | | | | | | |
| 4 | + | 5<br>7<br>8½ | H. F.<br>L. B.<br>H. F. | -<br>-<br>- | | | | | | | | Rabbit showed humoral immunity at 3 months and 4 months |
| 6 | + | 5½<br>6<br>6½ | L. B.<br>H. F.<br>C. P. | -<br>-<br>- | | | | | 7 | C. P. | - | Serial transfer successful; mouth free from herpes virus at 7 months |
| 6 | + | | | | | | | | | | | Serial transfer successful; origin of C. P. strain |
| | | | | | 7 | + | 14 | + | | | | Original rabbit probably immune |
| 3 | + | 1 | H. F. | - | 3 | - | 17 | + | | | | |
| 5 | - | 2½ | H. F. | + | | | | | | | | |
| 8 | + | | | | | | | | | | | Rabbit showed humoral immunity at 3 months |
| 4 | + | | | | 4 | - | 25 | + | | | | Serial transfer successful; origin of J. S. strain |
| 4 | + | | | | | | | | | | | Smears from mouth on fourth day showed no inclusion bodies |

TABLE II

CASES OF MISCELLANEOUS ORAL INFLAMMATION (CONTROLS)

| NAME OF PATIENT | NUMBER | AGE (YR.) | SEX | DIAGNOSIS | EXPOSURE | | DARK-FIELD EXAMINATION | | | | STAINED SMEAR | RABBIT CORNEAL INOCULATION | | | | | COMMENTS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | PRIMARY | | SUBSEQUENT IMMUNITY | | | |
| | | | | | COLD SORE | SORE MOUTH | TREPONEMAS | FUSIFORM BACILLI | VIBRIOS | SPIRILLA | | DAY OF DISEASE | RESULT | TIME (MO.) | VIRUS | RESULT* | |
| G. H. | 22 | 10 | M. | Canker sore | 0 | 0 | 0 | + | + | + | | 2 | + | 5<br>6<br>7 | L. B.<br>H. F.<br>C. P. | -<br>-<br>- | Reaction in rabbit's eye atypical<br>Serial transfer unsuccessful |
| L. R. | 23 | 11 | F. | Severe gingivitis | 0 | 0 | + | + | + | + | | 9 | + | 5<br>8 | H. F.<br>C. P. | -<br>- | Reaction in rabbit's eye atypical |
| P. H. | 24 | 7 | M. | Aphthous stomatitis† | 0 | 0 | | | | | | 2 | - | 1 | H. F. | + | |
| N. T. | 25 | 7 | F | Aphthous stomatitis | 0 | 0 | | | | | | 12 | - | 4 | H. F. | + | |
| M. T. | 26 | 2 | F. | Aphthous stomatitis | 0 | Case 25 | | | | | | 7 | - | 4 | H. F. | + | |
| R. K. | 27 | 2 | M. | Aphthous stomatitis | 0 | 0 | | | | | + | 4 | - | 5 | H. F. | + | |
| D. L. | 28 | 1½ | F. | Gingivostomatitis with exanthem | + | 0 | + | + | + | 0 | | 3 | ± | 3 | H. F. | + | Possibly an atypical case of acute infectious gingivostomatitis |
| D. S. | 29 | 4 | F. | Tonsillitis and stomatitis | 0 | 0 | | | | | | 6 | - | 5 | C. P. | + | |
| R. E. | 30 | 1½ | M. | Vincent's angina | 0 | 0 | + | + | + | + | + | 1 | - | 6 | H. F. | + | ✓ |
| L. M. | 31 | 6 | F. | Acute stomatitis | 0 | 0 | + | + | + | + | + | 8 | - | 2 | H. F. | + | |
| D. O. | 32 | 1½ | M. | Measles | 0 | 0 | 0 | + | 0 | 0 | | 2 | - | 1 | L. B. | + | ✓ |
| J. H. | 33 | ½ | M. | Gingivitis and dentition | 0 | 0 | 0 | 0 | 0 | 0 | | 3 | - | 1 | C. P. | + | ✓ |
| J. H. | 34 | 16 | M. | Stomatitis | 0 | 0 | | | | | | 3 | - | 1 | C. P. | + | |

*Positive (+) result indicates animal not immune. Negative (-) result indicates animal immune.

†See footnote on p. 152.

rabbit brain* was added to the serum and thoroughly mixed. White mice were injected intracerebrally with this virus-serum mixture within one-half to one hour (time unimportant). In most cases, four, but occasionally only three mice were injected with each serum-virus sample. Controls received the same virus emulsion diluted with an equal volume of normal saline. Usually a known positive neutralizing serum was retested with each new group of sera tested. The animals were observed daily for ten to twelve days. In order for a series of tests to be acceptable, the control animals must die between the fourth and eighth days, and the protected control animals must survive. Whenever the results were equivocal, which was seldom the case, the serum was retested, and if still equivocal it was so reported (±).

## ANALYSIS OF THE DATA

### A. Clinical Evidence:

1. One might expect to obtain a frequent history of exposure, either to someone with a "cold sore" or to a case of the disease in question. In 7 of the 21 patients (i.e., 33 per cent), there was a definite history of intimate exposure to someone with a herpes simplex lesion of the lip, and in 2 other patients (9.5 per cent) there was a known exposure to a case of acute infectious gingivostomatitis, making a total of 42.5 per cent of the cases which followed known exposure to the herpes simplex virus. On the other hand, only 1 (7.7 per cent) of the 13 control patients gave such a history of exposure.

2. The seasonal incidence of acute infectious gingivostomatitis should parallel the seasonal incidence of other types of herpetic infection in the same community. No accurate data on the seasonal incidence of "cold sores" in this locality during the course of this study could be obtained. However, it is a local clinical impression that "cold sores" in ambulatory patients occur more frequently in the summer when the predisposing factors of sunburn, chapping, windburn, etc., are most active. Sixteen, or 76.2 per cent, of the patients were observed in the six calendar months from April to October, which indicates a probable correlation of seasonal incidence.

3. There should be no basic incompatibilities between the known clinical effects of herpetic infection and the clinical features of this disease. No basic incompatibilities between the known clinical effects of herpes simplex virus disease and the clinical features of acute infectious gingivostomatitis have been observed. Known herpetic lesions and acute infectious gingivostomatitis have these fundamental features in common: they are superficial, usually occur in or near the mouth, run a self-limited course, and are free from complications. The striking difference in age incidence may harbor the explanation of the diversity of gross appearance, although in view of the fact that older children and adults are also occasional victims of acute infectious gingivostomatitis, other factors besides age are certainly operative. Among the other and as yet unappraised possibilities are route of inoculation, dose of virus, virulence of virus, and the state of immunity of the host. The lesions of

*The "known" strain of herpes simplex virus used throughout this study was the H. F. strain[12] in rabbit brain, kindly supplied by Dr. Rivers. This strain is highly neurotropic for rabbits.

"aphthous stomatitis" and the solitary "canker sore"* are grossly more suggestive of the usual activity of the herpes simplex virus than are the relatively diffuse lesions of acute infectious gingivostomatitis.

B. Bacteriologic Evidence:

1. It should be possible to demonstrate the presence of the virus in a high proportion of cases examined early in the course of the disease and this incidence should approximate 100 per cent with multiple examinations. In fifteen, or 79 per cent, of nineteen cases so examined, herpetic keratoconjunctivitis followed the first inoculation of the rabbit's eye. The result was never positive later than eight days after onset. Two of the four negative results were obtained on the eleventh and twelfth days of the disease, respectively. Thus, a single examination for the presence of the virus was positive in 89.5 per cent of those cases in which this examination was performed during the first eight days of the disease. All but one of the inoculated rabbits survived their infection. Eleven of these animals were subsequently inoculated with the known virulent H. F. strain of herpes simplex virus without a single positive reaction, whereas nonimmune control animals similarly and simultaneously inoculated died characteristically of herpetic encephalitis. These findings are very similar to those of Dodd, Johnson, and Buddingh.[7]

2. Conversely there should be a low incidence of positive results from rabbit corneal inoculations with material from other types of oral inflammation in children. In two, or 15.4 per cent, of thirteen control cases of stomatitis, an atypical reaction in the rabbit's eye developed following inoculation. After recovery these animals were immune to an active virulent strain of the herpes simplex virus. In the remaining eleven (84.6 per cent) controls, rabbit corneal inoculations were negative, although the animals were in every case later shown to be susceptible to corneal inoculations with the herpes simplex virus.

3. The normal child's mouth should also reveal a low incidence of positive examinations for the presence of the herpes virus. Nine normal healthy children, six boys and three girls, between the ages of 12 and 51 months, with negative past histories of lesions of the mouth, were selected to serve as normal controls. None of these children on the basis of direct rabbit corneal inoculation of scrapings from the gum margins was found to harbor the herpes virus.

4. Strains of virus isolated from cases of the disease should have the physical, pathologic, histologic, and immunologic characteristics of known strains of herpes simplex virus. Four strains of the virus were successfully isolated and studied.

(a) L. B. strain. Four successful passages of the virus were made, the first two in the rabbit's eye, the last two in the mouse's brain. Fol-

*Throughout this paper the term "aphthous stomatitis" is arbitrarily used to designate that disease characterized by the appearance of a number of small white round shallow ulcers of the mucous membrane of the mouth without any gingival involvement; whereas, the term "canker sore" is used to designate solitary circular ulceration of the oral mucous membrane.

lowing freezing and drying in vacuo the material was no longer active against the rabbit's eye.

(b) J. C. strain. Four successful passages through rabbits were accomplished. The fifth passage material after freezing and drying in vacuum was no longer active.

(c) C. P. strain. This strain of herpes virus was fatal to rabbits, with two exceptions, from its first isolation. Its virulence for rabbits increased after the first few passages. The original animal after corneal inoculation died of encephalitis in sixteen days, whereas the fifth and seventh passage animals died in seven days after the same route of administration.

(d) J. S. strain. Six successful serial passages through rabbits were accomplished with this strain. The sixth passage was into the scarified cornea of a rabbit. Fig. 1 shows the acidophilic intranuclear inclusion bodies found at the sites of the corneal scarifications.

5. Known strains of herpes simplex virus or material from recognized herpes simplex lesions (cold sore) should, upon inoculation, produce acute infectious gingivostomatitis in susceptible subjects.

S. D., a white girl 12 months old, was offered as a volunteer for inoculation with material from a typical "cold sore" of the lip of an otherwise healthy adult. S. D. had never had a sore mouth. She had had varicella and had been immunized against diphtheria. She had not been vaccinated for smallpox. She had six teeth, the four upper incisors and the two lower central incisors. No visible deviations from the normal were found in her mouth. Dark-field examination of material from the gingivodental sulcus revealed no treponemas, vibrios, spirilla, or type I fusiform bacilli. There were moderate numbers of type III and occasional type II fusiform bacilli. The blood serum contained no herpes virus neutralizing properties.

The gum above S. D.'s upper left central incisor was scarified with a sterile needle and directly inoculated with material from two of the intact herpes simplex vesicles. For two days S.D. remained well and the gingival scarification appeared to be healing. On the third day her rectal temperature rose to 101.6° F. The following morning she would not eat. The rectal temperature was 101.4° F. At the site of the inoculation there was an irregular yellow erosion 4 mm. in diameter. All of the gums were red and slightly swollen. There was a little marginal gingival ulceration behind the upper incisors and a small round white ulcer of the lower lip where it touched the lower left central incisor. There were several small slightly elevated areas on the anterior pillars, two of which were ulcerated. The tonsils were slightly injected and the anterior pillars very red. The submaxillary lymph nodes were somewhat swollen. The blood serum still contained no herpes virus neutralizing properties. She vomited twice during the night. The next day the rectal temperature was 101.6° F. There was pain on eating. The breath had become very foul. Solitary small white ulcers had appeared on the upper and the lower lip. The upper gums adjacent to the teeth were red and swollen and loose but not bleeding. The margin ulceration had extended about 2 mm. back on to the roof of the mouth. Dark-field examination of scrapings from the gingival lesions gave the same findings as before, except that there were numerous pus cells present. A stained gingival smear revealed many spindles and a few pus cells. Examination of the blood revealed 14,300 leucocytes per cubic millimeter, 54 per cent of which were polymorphonuclear

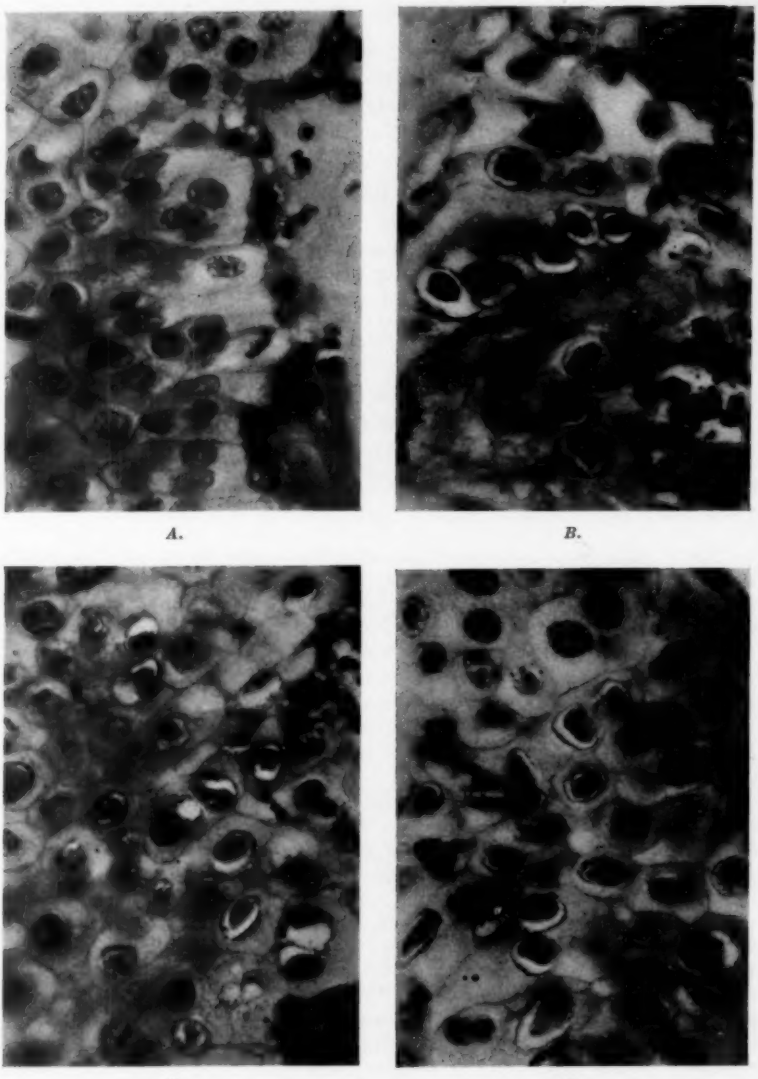

Fig. 1.—Photomicrographs of nuclear changes in rabbit's cornea induced by scarification with and without inoculation of various strains of herpes simplex virus.

*A*, Control. Section of normal rabbit's cornea twenty-four hours after scarification. Note hyperplasia of corneal cells which have filled the defect caused by the trauma. No intranuclear inclusion bodies. (×930).

*B*, Herpes simplex virus, H. F. strain. Intranuclear inclusion bodies in rabbit's cornea at twenty-four hours. (×930).

*C*, Herpes simplex virus, J. S. strain. Rabbit's cornea twenty-four hours after inoculation. Note margination of deeply staining basophilic chromatin separated by clear space from the acidophilic intranuclear inclusion bodies.

*D*, Herpes simplex virus, C. P. strain. Note successive steps of nuclear changes from simple hyperplastic state as in *A* above to well-developed inclusions. (×930).

neutrophiles, 41 per cent lymphocytes, 4 per cent monocytes, and 1 per cent eosinophiles.

There was no fever after the fourth day of the disease. Nine days after the original inoculation and six days after the onset of the disease the clinical picture was absolutely typical of acute infectious gingivostomatitis. Dysphagia was marked. The gums were swollen, intensely inflamed, tender and loose, and bled easily. Small white ulcers studded the insides of the lips, the tongue, and the anterior pillars. The marginal ulceration was unchanged. The breath was foul and the submaxillary lymphadenopathy was striking. Dark-field examination and stained smear were unchanged.

On the seventh day of the disease healing began and was complete fifteen days after the onset. On the ninth and thirteenth days the blood serum contained questionable herpes virus neutralizing properties.

Two weeks later, dark-field examination of material from the gingivodental sulcus showed only a few type II and a moderate number of type III fusiform bacilli. The blood serum contained unquestionable herpes virus neutralizing properties. The virus of herpes simplex was still present in the mouth. The right upper gum was scarified and inoculated with the J. C. strain of herpes virus. The scarifications healed and no symptoms or lesions developed, whereas a rabbit inoculated with the same virus at the same time developed typical herpetic keratoconjunctivitis and after recovery was immune to known virulent strain of the herpes virus.

On the same day as the primary inoculation of S. D., R. M., a white boy 6 years old, was inoculated into the scarified gum with fluid from one of the W. B. herpes simplex lesion vesicles. This boy's past history was negative for acute infectious gingivostomatitis or other soreness of the mouth. Dark-field examination of material from the gingivodental sulcus revealed an occasional fusiform bacillus and numerous spirilla. The blood serum did not contain herpes virus neutralizing properties. Four days later the site of inoculation showed a little white debris. There were no other changes in the mouth. There was no fever. On the sixth day, the only change was the appearance of a small white ulcer inside the lower lip on the left side which healed in a few days.

A number of inoculations of the scarified corneas of white rabbits were made during the course of this case study. In all cases where the resulting keratoconjunctivitis was clinically typical of the presence of the herpes simplex virus, its specificity was checked by subsequent similar inoculations with the H. F. and C. P. strains. In every case the convalescent animals were immune to these strains, whereas simultaneously inoculated normal control rabbits became infected. Similarly negative results were proved not to be caused by herpes virus immunity by subsequently infecting the animal with a known strain of herpes virus. The results of these inoculations may be summarized as follows:

1. The virus was present in the vesicle fluid of the herpes simplex lip lesion on the first day.

2. The virus was not present in gingivodental groove scrapings from S.D. just before she was inoculated but was present in the oral lesions five and twelve days later. The virus was also present thirty-four days after the primary inoculation when her mouth had appeared to be entirely well for sixteen days. However, six days later the virus was not present.

3. The virus was not present in scrapings from the gingivodental sulcus of R. M., just before he was inoculated, but was present in material from the ulcers and gums six days later.

This evidence indicates that fluid from a herpes simplex vesicle containing the herpes simplex virus upon inoculation into the gum of a

1-year-old child was followed by the development of an illness typical of acute infectious gingivostomatitis. The inoculated child manifested no humoral immunity to the herpes virus before the inoculation but after recovery did have such an immunity and was also refractory to oral inoculation with a known virulent case-isolated strain of the virus. The virus, absent from the mouth before the original inoculation, was recovered during the illness and was still present in the mouth two weeks after complete clinical recovery but was absent another week later. At no time before, during, or after the illness were treponemas, spirilla, or vibrios found in the lesions or in the gingivodental sulcus. Fusiform bacilli were constantly present. An older child simultaneously inoculated, and who had no humoral immunity, developed no widespread oral lesions or constitutional symptoms but did develop two shallow white virus-containing ulcers indistinguishable grossly from ordinary "canker sores."

C. Histologic Evidence:

1. Acidophilic intranuclear inclusion bodies recognized as characteristic and perhaps as specific of herpes simplex virus infection should be present in the lesions of the disease and be absent from oral lesions of other kinds. It has been shown repeatedly that in experimental herpes simplex virus infection the inclusions are most abundant during the early stages of the infection and may be very difficult to find later.[12, 13, 14, 15] Only four of the present series of cases were seen as early as the third day of the disease. Biopsy of the lesions in these cases was contemplated but not done because the procedure was not deemed entirely without danger to the child. The device of fixing, staining, and examining scrapings from the lesions for the presence of inclusions was employed with negative results on the fourth day of the illness in one case. Negative results were obtained in four other cases similarly examined later in the course of the infection. These findings lend no positive support to the hypothesis of herpes virus etiology, but neither are the negative implications in any sense conclusive proof that herpetic inclusions are not present in the early lesions of the disease.

2. Acidophilic intranuclear inclusion bodies should be present in the lesions induced in experimental animals with material from the lesions of the disease. The inclusions were regularly, abundantly, and easily demonstrated in every instance in which they were sought for in twenty-four-hour rabbit corneas successfully inoculated from lesions of the disease (Fig. 1). In corroboration of Lauda's[16] experience, we were not able with regularity to find inclusions in the brains of rabbits or mice dead of herpetic encephalitis and thus did not frequently employ this examination of such material.

D. Immunologic Evidence:

1. Humoral immunity to the herpes simplex virus should develop during the course of the disease. In ten cases the serum was examined for the presence of herpes virus neutralizing properties on or before

the seventh day of the disease. In seven cases no immunity was present. In three cases immune bodies were present. In nine of these ten cases the serum was subsequently examined one or more times and in every instance in at least one of the subsequent examinations the serum contained indisputable herpes virus neutralizing properties. In one case thirty-nine days after the onset and in another case five months after the onset questionable results were obtained. Table III summarizes these findings and indicates the intervals between drawing and examining the blood specimen and how the serum was stored during these intervals, whether in the liquid state or lyophilized.

TABLE III

VIRUS NEUTRALIZATION TESTS

| CASE NUMBER | AGE (YR.) | SEX | FIRST TEST | | | | SUBSEQUENT TESTS | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | DAY OF DISEASE | BLEEDLYOPHILE INTERVAL (DAYS) | MONTHS STORED | RESULT | DAYS AFTER ONSET | BLEEDLYOPHILE (DAYS) INTERVAL | MONTHS STORED | RESULT |
| 1 | 1 | F. | 4 | Wet | 1/15 | – | 30 | 2 | 4½ | + |
| | | | | | | | 75 | 2 | 3 | + |
| 3 | 1 | M. | 2 | 1 | 4½ | – | 33 | 1 | 3½ | + |
| 4 | 2 | M. | 5 | 0 | 4 | – | 12 | 1 | 3 | + |
| | | | | | | | 39 | 1 | 3 | ± |
| 5 | 8 | F. | 7 | 1 | 1½ | – | 35 | Wet | 1/30 | + |
| 7 | 15 | F. | 4 | Wet | 1/3 | + | | | | |
| 9 | 1 | F. | 6 | 2 | 4½ | + | 35 | 1 | 3½ | + |
| 11 | 2½ | F. | 3 | Wet | 1/6 | – | 35 | Wet | 1 | + |
| | | | | | | | 150 | 1 | 2½ | ± |
| 16 | 1½ | F. | 7 | 1 | 4 | + | 14 | 1 | 4 | + |
| 17 | 1½ | M. | 3 | 1 | 4 | – | 17 | 3 | 2 | + |
| 20 | 1½ | F. | 4 | Wet | 2/3 | – | 25 | Wet | 1/30 | + |

2. Convalescent children might be refractory at least temporarily to inoculation with herpes simplex virus. Four cases were inoculated with the C. P. strain one, one and one-half, two, and seven months, respectively, after the onset of the disease. In no case did any symptoms or lesions develop. The inoculations were made by scarifying the upper anterior gum with a sterile needle and rubbing the virus (mashed rabbit brain) thoroughly into the abrasion. The gums of two other children were similarly abraded and rubbed without the application of virus. All the abrasions healed promptly. The activity of the virus for rabbits was proved by simultaneous rabbit corneal inoculations. However, the virus used may have lost its pathogenicity for humans.[17]

3. Presumed susceptibles (i.e., normal young children) usually should not have humoral immunity to the herpes simplex virus. The same nine normal healthy children whose mouths were found not to harbor the herpes simplex virus (see Bacteriologic Evidence, Part 3) were tested at the same time for humoral immunity. Six were found not to have herpes virus neutralizing substances in the serum, whereas in three

cases a positive result was obtained. In none of these cases was there a positive past history of oral inflammation or of herpes simplex lesions. Zinsser and Tang[18] found 25 per cent of sixteen hospitalized children between 3½ months and 6 years of age were neutralizers, whereas Weyer[19] found 14 per cent neutralizers in a group of twenty-eight children less than 5 years old. The composite result indicates that approximately 20 per cent of children under 5 years of age harbor serum herpes virus neutralizing bodies.

## SUMMARY

One may demonstrate with a high degree of regularity by means of single direct rabbit corneal inoculations of material from the oral lesions of acute infectious gingivostomatitis that there is an agent present in this material which is indubitably the herpes simplex virus. Proof of the identity of this agent is presented in the preceding sections of this paper but may be summarized as follows:

1. The clinical course of the lesion in the inoculated rabbit's eye is typical of herpetic keratoconjunctivitis produced by known strains of herpes simplex virus.

2. Transfer of the infection to other rabbits in series is easily accomplished.

3. The lesion in the rabbit's eye contains intranuclear acidophilic inclusion bodies, indistinguishable from the inclusions produced by known strains of herpes simplex virus.

4. The infected animals after recovery are immune to inoculations with known virulent strains of herpes simplex virus.

5. The agent on several occasions has been obtained free of bacterial contamination from the infected rabbit's eye and carried in serial inoculations of rabbits and mice for months.

6. The agent so obtained produces uniformly the typical clinical picture of fatal herpetic encephalitis when injected intracerebrally into rabbits or mice.

7. The agent may be preserved in an active state for considerable periods of time when the infected brain is refrigerated in 50 per cent glycerol.

The herpes simplex virus is not only present in the lesions of the disease but is the etiologic agent of acute infectious gingivostomatitis. Granting the accuracy of the findings reported in this paper, no other interpretation is plausible. That the presence of the virus in the lesions of the disease is neither incidental nor accidental but is the result of a true etiologic relationship is attested to by the facts described in detail in the preceding sections of this report, which may be summarized as follows:

1. The virus is not commonly present during childhood in the normal mouth, nor in mouths which are the sites of other types of inflammation

such as aphthous stomatitis, canker sores, Vincent's angina, measles, etc., whereas the virus may be found on a single examination during the first few days of the infection in approximately 90 per cent of the cases of acute infectious gingivostomatitis.

2. Humoral immunity, as indicated by virus neutralization tests, is constantly present after the disease has run its course but is not commonly present during the early stages of the disease.

3. Intimate exposure to a source of herpes virus was known to have occurred in over 40 per cent of the cases of the disease, whereas only 8 per cent of the cases of other types of oral inflammation gave a history of exposure to active herpetic lesions.

4. Finally, a typical attack of acute infectious gingivostomatitis in a 1-year-old child followed inoculation of this child's mouth with fluid from the vesicles of a herpes simplex lesion on the lip of an adult.

Thus the criteria necessary to prove virus etiology as enunciated by Rivers[10] have been completely satisfied and the conclusions reached by Dodd, Johnson, and Buddingh[7] have been verified.

## CONCLUSIONS

1. Acute infectious gingivostomatitis (Vincent's stomatitis, Vincent's angina, ulcerative or ulceromembranous stomatitis, fusospirochetal stomatitis, trench mouth) is caused by the herpes simplex virus.

2. The disease should now be known as acute *herpetic* gingivostomatitis.

3. The fusospirochetal organisms play no essential primary or secondary role in the pathogenesis of the disease.

4. Lesions containing the herpes simplex virus are common sources of the infection for young children.

5. No specific treatment for the disease is known. General supportive and local hygienic procedures may be relied upon to be followed by complete recovery.

I am indebted to Dr. S. J. McClendon for the opportunity of studying several cases from his practice, to Dr. H. S. Summerlin for the preparation of the photomicrographs and all histologic material, and to Mrs. P. W. Ferrall for technical assistance.

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# IMMUNITY TO WHOOPING COUGH AS JUDGED BY A SKIN TEST ON RABBITS

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THE question as to whether a human being has an immune response to whooping cough has been determined heretofore by agglutination reactions, complement fixation reactions, mouse protection tests, and opsonocytophagic tests. The literature reveals many contradictory results. As far as *agglutination reactions* are concerned, Mishulow, Klein, Liss, and Leifer's[1] results showed a higher, longer lasting titer after whooping cough than after immunization, whereas Miller and Silverberg[2] found a higher, longer lasting titer after immunization than after an attack of whooping cough. My results in a small series of cases with the rapid agglutination test,[3] parallel those of Miller and Silverberg. Thus, four to eight weeks after the onset of whooping cough, the agglutination test becomes positive and remains positive for only six to twelve months. On the other hand, after immunization, 11 out of 19 children gave positive agglutination tests for three to five years. *Complement fixation reactions* were found by the author[4] to remain positive for only five to eight months after immunization was complete. After an attack of pertussis, the complement fixation reaction remained positive for less than a year in about 90 per cent of the cases. *Opsonocytophagic reactions,* while used recently by Rambar, Howell, and Goldman[5] to judge the immune response, have been considered by Lichty, Slavin, and Bradford[6] subject to so many nonspecific variations as to be valueless. These serologic tests labor under the disadvantage of being considered tests of "nonprotective antibodies." *Mouse protection tests,* which, on the whole, parallel the serologic tests, have been extensively used because they presumably measure protective antibodies. Unfortunately the number of mouse protection tests recorded in the literature is still so few that final and unqualified conclusions are not justified. On the whole, however, the results of mouse protection tests seem to parallel the biologic test of intimate exposure. The technique of performing the test has varied in the hands of different authors. Intraperitoneal injections,[7, 8, 9, 10] intranasal instillation,[11, 12] and intratracheal instillation [13, 14] have been recommended. While there seems to be a fairly accurate correlation between immunity as judged by the biologic test of intimate exposure and the mouse protection tests, there are unaccountable variations in the virulence of *H. pertussis* which mask the results. Furthermore, the tests require a large number of animals and a difficult technique.

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*Skin testing on human beings* to determine immunity with various endotoxic and exotoxic factors of *H. pertussis* has been adequately reviewed by the author in a recent publication.[15] Suffice it to say that like most bacterial allergic skin tests, results are confusing and disappointing.

For this reason, before attempting further skin tests on human beings, it seemed desirable to perform preliminary skin tests on rabbits. Döld[16] had originally recommended the intracutaneous injection of living *H. pertussis* as a valuable bacteriologic differentiation of *H. pertussis* from *H. influenza*. Gundel and Schlüter[17] standardized the test by injecting 0.2 c.c. of a 5 billion to the cubic centimeter suspension of living *H. pertussis* in normal saline intradermally into the recently epilated skin of a white rabbit. Twelve to eighteen hours after injection the site showed a circular, slightly prominent infiltration, which became bluish after another twelve hours. The infiltration decreased while the bluish discoloration increased, until after twenty-four to forty-eight hours hemorrhagic necrosis was evident. Ulceration, scab formation, and sloughing of the scab occurred within four days after the injection. Kendrick, Miller, and Lawson[18] modified this test by injecting 0.1 c.c. of a 1 billion to the cubic centimeter saline suspension of living organisms. Sauer[27] advises that vaccine manufacturers should take cultures of *H. pertussis* out of production as soon as they fail to produce typical necrosis, as measured by this test.

I can find no record that the neutralization of this necrotic reaction by the simultaneous injection of animal or human sera has been used as an evidence of immunity. Unpublished work by Roberts[19] claimed that a rabbit immunized with "detoxified antigen" was able to resist the necrotizing effect of intradermal injections of live *H. pertussis*. Long[20] stated that animals immunized with living bacilli produced a good immune serum with "definite antibacterial power, as is easily demonstrated by the prevention of the spread of an *H. pertussis* lesion in the skin of a rabbit." Furthermore, Long stated that animals immunized with vaccines produced a serum which could not protect from this skin necrosis. On the other hand, North and co-workers[21] claimed to have prevented skin necrosis with serum from rabbits immunized with vaccines. The contradictory results obtained by these workers[20, 21] may have been due to differences in the doses used. Unfortunately neither author gave details of the dosages used.

## PART I. PROCEDURE

Four New Zealand red, full-grown rabbits were given daily doses of 1 to 2 c.c. of an *H. pertussis* vaccine, phase I, containing from 15 to 30 billion organisms per cubic centimeter until they had received 200 billion organisms. One to two weeks later, blood was withdrawn from the heart of these animals and pooled for the preparation of "immune serum." This serum gave a 4+ complement fixation, a 4+ rapid agglu-

tination test, and a strong mouse protection titer, and was used in Part II of this study. Two weeks after this the rabbits were epilated, and intradermal injections were given, using 0.2 c.c. of a 2 billion to the cubic centimeter concentration of two different suspensions, one "washed," and the other "unwashed." A forty-eight-hour growth of fresh, virulent, phase I strain of *H. pertussis* on a Bordet-Gengou slant was scraped off with a little saline, suspended in 10 c.c. of saline, centrifuged for one-half hour, and the supernatant liquid decanted off. This washing was repeated three times, and the final sediment was resuspended in saline at a concentration of 2 billion organisms to the cubic centimeter. The resultant suspension of living organisms is referred to as "washed." A similar forty-eight-hour growth was scraped off with saline at a concentration of 2 billion organisms to the cubic centimeter. The resultant suspension is referred to as "unwashed."

Table I

The Effect of Vaccination of Rabbits on Their Ability to Resist the Skin Necrotizing Effect of Intradermal Injection

| Time after Intradermal Injections (hr.) | Control Unvaccinated Rabbits | | Immunized Vaccinated Rabbits | |
|---|---|---|---|---|
| | Washed Suspension | Unwashed Suspension | Washed Suspension | Unwashed Suspension |
| 36 | Faint Purple | Purple<br>White<br>Red | Faint Red | Faint Red |
| 60 | Purple | Purple<br>Red | Red | Faint Purple |
| 84 | Purple | Black<br>Red | Red | Faint Purple |
| 108 | Black<br>Purple | Black<br>Red | Red | Red |
| 132 | Black<br>Necrosis | Black<br>Necrosis | Red | Red; slight induration |
| 156 | Black<br>Necrosis | Scab | Red | Red; slight induration |
| 228 | Scab | Scab | Red | Red |

Daily observation of the sites of the intradermal injections resulted in the figures shown in Table I. This experiment was carried out in triplicate. The control rabbits showed an area 1 cm. in diameter, purplish at first, changing by the third day to black in color. By the fourth day, necrosis was evident; by the fifth, ulceration and scab formation. The difference in necrotizing power of the "washed" and "unwashed" suspensions seems merely one of degree. The "unwashed" produces an earlier purplish discoloration, which undergoes necrosis and scab formation, on the average, one day earlier than the "washed." The rabbits immunized by vaccine injections showed an area 1 cm. in diameter and erythematous, which became slightly indurated by the fifth day. There was no necrosis, and no ulceration or scab formation.

*Discussion.*—Rabbits vaccinated with 200 to 800 billion of *H. pertussis* vaccine were able to resist the skin-necrotizing power of intradermal injection of 0.2 c.c. of a 2 billion to the cubic centimeter concentration of "washed" and "unwashed" living suspensions of *H. pertussis.* The

controls showed no such resistance; their skin developed hemorrhagic necrosis, ulceration, and scab formation. Due to lack of facilities, no effort was made to determine the minimum dosage of vaccine necessary

Fig. 1.—Intradermal test in control rabbit, showing ulceration, necrosis, and scab formation.

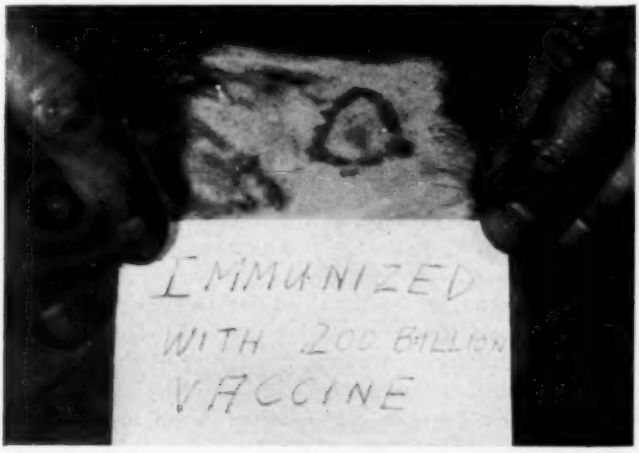


Fig. 2.—Intradermal test in rabbit previously immunized with 200 billion vaccine, showing erythema but no ulceration, necrosis, or scab formation.

to protect the rabbits. Whether the rabbits may be said to have acquired antitoxic immunity to pertussis is a theoretical question which cannot be discussed here; the work of Flosdorf, Dozois, and Kimball[22] has recently emphasized the difficulties in work with the toxins of *H. pertussis*.

PART II

The second part of this study was designed to test the protective power of rabbit immune serum, horse immune serum, and various human immune and nonimmune sera against the skin-necrotizing effect of

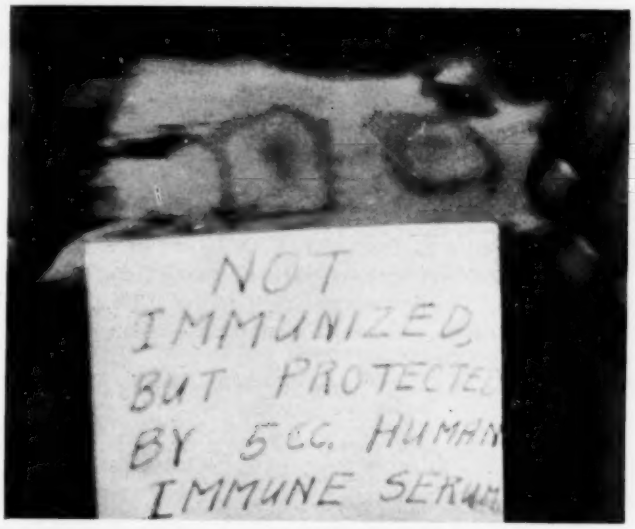


Fig. 3.—Intradermal test in rabbit protected by simultaneous administration of 5 c.c. of human immune serum, showing erythema but no necrosis, ulceration, or scab formation.

Fig. 4.—Intradermal test in rabbit who had received 5 c.c. of human nonimmune serum (from 6-month-old infant), showing ulceration, necrosis, and scab formation.

intradermal injection of 0.2 c.c. of an "unwashed" 2 billion to the cubic centimeter saline suspension of living *H. pertussis.*

*Procedure.*—Full-grown, New Zealand red rabbits were epilated. Two control animals received only the intradermal injection of 0.2 c.c. of the unwashed 2 billion to the cubic centimeter suspension. Two more, who had been immunized previously in the manner described in Part I with from 200 to 800 billion of *H. pertussis* vaccine, also received only the intradermal injection. The other rabbits each received simultaneous injections of the necrotizing dose of *H. pertussis,* and of the various sera to be described. The injection of sera was done subcutaneously in different areas of the back. Experiments were carried out in duplicate only, due to lack of facilities.

An analysis of the results in Table II shows:

1. Rabbits injected with from 200 to 800 billion of *H. pertussis* vaccine within a period of one month are protected from the skin-necrotizing effect of the intradermal injection of 0.2 c.c. of a 2 billion to the cubic centimeter "unwashed" saline suspension of live *H. pertussis* organisms.

2. Of animal immune sera, horse serum gives no protection; rabbit serum very slight.

3. Human immune serum, prepared by injecting a human being with a previous history of whooping cough with a trillion of *H. pertussis* vaccine within a period of 1 month, gives complete protection.

4. Human convalescent serum, human "stimulation" serum, and human "combined immunization" serum give moderate protection. Hemorrhagic areas with marked infiltration form, but the typical end-point of necrosis, ulceration, and scab formation is missing.

5. Human "infant" serum in one case, and human "cord blood" serum in another case give no protection.

## DISCUSSION

Due to limitation of facilities, only small groups of animals could be employed. If the results can be duplicated in a larger number of animals, certain interesting deductions can be drawn.

Immunity in whooping cough is "humoral," and passive protection by transmission of large doses of human immune serum should be practicable. The author[23] and McGuiness, Bradford, and Armstrong[24] have reported excellent results in prophylaxis and encouraging results in the treatment of whooping cough with a human immune serum. Zinsser, Enders, and Fothergill[25] objected to the use of human serum, on the ground that no "humoral" immunity in whooping cough has ever been demonstrated. If the results of this paper are corroborated, "humoral" immunity has been demonstrated.

Toomey[26] and Toomey and Takacs[28] injected 20 c.c. of a hyperimmune horse serum with an agglutination titer of 1:40,000 into each of 20 patients with whooping cough. There was a sharp increase in parox-

Table II

Serum Protection Effect on Skin Necrosis Test

| Hour After Intradermal Injection | 0.2 cc. Of 2 Billion to the cc. Suspension of Living H. Pertussis | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Control | Vaccinated 2 Years Previously | 5 cc. Rabbit Immune Serum | 5 cc. Horse Immune Serum | 5 cc. Human Immune Serum | 5 cc. Human Convalescent Serum | 5 cc. Stimulation Serum | 5 cc. Combined Immunization Serum | 5 cc. Infant Serum | 5 cc. Cord Blood Serum |
| 2 | Purple White Red | Slight Red | | | Slight Red | Red | Red | | | |
| 3 | Purple Red | Slight Purple | Purple | | Slight Red | Purple | Purple | | | |
| 4 | Black Red | Slight Purple | Purple | Purple | Slight Red | Purple | Purple | Purple | | |
| 5 | Black Necrosis | Red | Purple | Black | Slight Red | Purple | Purple | Purple | | |
| 6 | Scab | Red; slight induration | Black | Scab | Slight Red | Purple | Purple | Purple | Black | Black |
| 7 | Scab | Red; slight induration | Black | Scab | Slight Red | Purple | Purple | Purple | Scab | Scab |
| 8 | Scab | Red | Scab | Scab | Slight Red | Purple | Purple | Purple | Scab | Scab |
| 9 | Healing | Red | Healing | Healing | Slight Red | Purple | Purple | Purple | Scab | Scab |
| Protection | None | Complete | Slight | None | Complete | Moderate | Moderate | Moderate | None | None |

1. Rabbit immune serum is the pooled serum referred to in Part I, which was withdrawn from rabbits that had been vaccinated with 200 to 800 billion of *H. pertussis* vaccine in the course of one month. Agglutination was 4+.

2. Horse immune serum was prepared by the Lilly Research Laboratories by intracutaneous injections of live organisms. Agglutination was 3+.

3. Human immune serum was withdrawn from a 16-year-old boy with a history of pertussis in childhood, who had received 1 trillion of *H. pertussis* vaccine in one month and was bled two weeks after the last injection. Agglutination was 4+.

4. Human convalescent serum was withdrawn from a 54-year-old woman with a history of pertussis in childhood, who had had a typical second attack of whooping cough for a period of seven weeks at which time blood was withdrawn. Agglutination was 3+.

5. "Stimulation serum" was the pooled product withdrawn from children who had been immunized with 80 billion of Sauer vaccine three to five years before and had received from 10 to 20 billion vaccine as a stimulating dose two weeks before blood was withdrawn. Agglutination was from 3+ to 4+ on various samples.

6. "Combined immunization" serum was the pooled blood withdrawn from infants who three months before had received 100 billion of pertussis vaccine in five monthly doses in combination with diphtheria and tetanus toxoid. The agglutination was from 3+ to 4+ on various samples.

7. "Infant" serum was withdrawn from a 6-month-old child with gastrointestinal intoxication, who had never had whooping cough. Agglutination was negative.

8. "Cord blood" serum was withdrawn from the cord of a newborn infant, whose mother was in the eighth week of a typical whooping cough. Agglutination test was negative.

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ysms and whoops and no curtailment of the disease. This poor result in treatment is explainable by the results demonstrated in this article; horse immune serum lacked the antiskin-necrotizing immune body contained in human serum. In general, serologic tests such as agglutination titers seem to run parallel to protective antibodies in pertussis;

yet animal sera may have high agglutination titers with practically no antiskin-necrotizing immune body.

If other specimens of cord blood from babies delivered of mothers suffering from pertussis fail to prevent the skin-necrotizing reaction, then the conclusion is justifiable that placental transmission of whooping cough antibodies does not exist.

## CONCLUSION

A practical test has been devised to demonstrate the presence of neutralizing bodies in serum. The test is positive in sera which have other antibodies in high titer: agglutination reactions, and complement-fixing antibodies. There is strong reason to believe that sera which can protect rabbits completely from the necrotizing effect of large doses of *H. pertussis* can also protect the individual from clinical pertussis. The demonstration of this must await mass studies of intimate exposures to clinical pertussis of individuals possessing such antibodies.

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# THE INITIAL RESPONSE TO IMMUNIZATION WITH DIPHTHERIA AND TETANUS ALUM TOXOID

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THE value of tetanus antitoxin used routinely in the wounded would seem to be well established in military life. But in civil life there are several factors which may lead one to be dissatisfied with the status of tetanus prophylaxis by the antitoxin method. In part, these are the difficulty of deciding in which instances it should be used, the fear of an anaphylactic type of reaction, the possibility of inducing sensitization where it does not already exist, and the more than occasional failure of the usual prophylactic dose of antitoxin to prevent tetanus.

The impossibility of deciding with accuracy when to give tetanus antitoxin is illustrated by two cases of tetanus which came to our attention recently. In one, a 3-year-old boy, living in a country town, injured the end of one finger slightly when a screen door closed on it. The injury was sustained indoors. Little was thought of it until fourteen days later when the first symptoms of tetanus appeared. In the other case, also in a child, there was neither history nor evidence of injury of any sort. Such cases are not unusual and are mentioned again simply to illustrate the well-known fact that insignificant injuries are sufficient to afford a portal of entry for tetanus.

We know, furthermore, that the usual practice of giving 1,500 units of antitoxin by no means affords protection in all cases, even when given early. As is indicated in the report of Kirtley,[1] numerous cases of tetanus have occurred in spite of this routine procedure, particularly where the wound has not been adequately cleaned. One of us (F. S. S.) recalls the high incidence of fatal tetanus among the school children victims of the Murphysboro tornado in 1925 despite field prophylaxis with tetanus antitoxin.

When the work of Ramon and others indicated that it was possible actively to immunize humans against tetanus by the use of toxoid, an important step had been taken. The value of such immunization to military groups was apparent and resulted in compulsory immunization in the French army in 1936. After a period of study it was also recommended in the British Army in 1938, and 90 per cent of the personnel was immunized on a voluntary basis. In this country tetanus toxoid has been given certain groups of adults and children. Recently it has become routine in the army and navy, the army using plain toxoid and the

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navy alum toxoid. Alum toxoid is also in use at Annapolis where over 3,000 men have been immunized, as reported by Hall.[2] Other reports deal with the immunization of infants and children or with the immunization of allergic individuals in whom the avoidance of tetanus antiserum seemed desirable. This desire to avoid serum, incidentally, had led us years ago to select children from our Allergy Clinic for the use of diphtheria toxoid shortly after its introduction into Canada.

The question arises of why we should not attempt to immunize all children against tetanus. If we could do so, we might have a more satisfying solution to the problem of tetanus prophylaxis than the present use of antitoxin. We have educated our patients to expect posttraumatic antitoxin, and the possibility of legal difficulties if it is omitted may have contributed more to its use than has its demonstrable effectiveness.

The present study was undertaken in order to afford additional data with which to clarify the response to active immunization. In 1937, we began the use of combined diphtheria and tetanus alum toxoid in the infants attending the Children's Allergy Clinic at the University of California Hospital. They tolerated the antigen well, and the following year its use was extended to a group in the Well-Baby Clinic. Up to the present time over 600 infants under 1 year of age have received such prophylaxis. This, at first, consisted of three injections of combined diphtheria and tetanus alum toxoid of 1 c.c. each, given at intervals of one month. Recently, we have increased the interval to two months. Two months or more after the last injection a Schick test was made and blood obtained by venipuncture for a determination of its tetanus antitoxin content by guinea pig assay. This report deals with 242 such assays. In this method varying amounts of the patient's serum are mixed with a fixed amount of a National Institute of Health standard tetanus toxin and injected into guinea pigs. The survival of a guinea pig indicates an excess of serum antitoxin for the level tested. Table I illustrates this method of assay.

The principle of active immunization against tetanus calls for the establishment of a basic immunity by such preliminary injections of toxoid. As is indicated in Fig. 1, no antitoxin is present to start with and the first injection does not result in appreciable antitoxin formation, but subsequent injections do. The peak of the initial rise probably varies in the time of its appearance with the number of injections and the interval between them. In our series, it apparently tends to occur about two months after the last injection. In the following months there is a gradual fall to a level which, while low, can be readily demonstrated. This residual antitoxin probably affords some degree of protection, especially against cryptogenic infection. Following likely exposure, however, another injection of toxoid is given, and a rapid and marked

TABLE I

METHOD OF ASSAYING SERUMS FOR TETANUS ANTITOXIN AFTER IMMUNIZATION

| | MIXTURE INJECTED | SYMPTOMS OF TETANUS IN GUINEA PIGS | | | | | RESULT | CONCLUSION |
|---|---|---|---|---|---|---|---|---|
| | | 24 HR. | 48 HR. | 72 HR. | 96 HR. | 120 HR. | | |
| Case A | 0.1 c.c. serum A plus 0.5 mg. tetanus toxin | 0 | 0 | + | ++ | ++ | Survived | 1.0 unit of antitoxin present per c.c. Serum A |
| Case B | 0.1 c.c. serum B plus 0.5 mg. tetanus toxin | ± | ++ | +++ | ++++ | Dead | Died in less than 120 hours | Less than 1.0 unit antitoxin present per c.c. Serum B |
| Case C | 0.1 c.c. serum C plus 0.5 mg. tetanus toxin | 0 | 0 | 0 | 0 | 0 | No tetanus | More than 1.0 unit antitoxin present per c.c. Serum C |
| Control | 0.1 unit (0.02 c.c.) standard tetanus antitoxin, plus 0.5 mg. tetanus toxin | ± | ++ | ++++ | Dead | | Died in 96 hours | Satisfactory control |

The possible variation in animals is such that the test animal must do significantly better than the control animal to warrant the conclusion that the same amount of antitoxin is present. On this basis the serum of Case A has 0.1 unit of antitoxin per 0.1 c.c. of serum, or 1 unit per c.c., and Case B has less than this amount.

antitoxin response is assumed to occur as a result, even if it be years later. Such a recall injection can also be given at regular intervals of several years in the absence of exposure. Published reports of cases in adults and older children have shown the recall levels to be considerably higher than the levels reached in the initial response and to occur so rapidly that within one week effective amounts of antitoxin have been attained. This is within the usual incubation period of tetanus, a matter of seven to fourteen days. It should be pointed out that this report deals with initial responses only and does not indicate what levels could be reached in the anamnestic reaction after the recall injection.

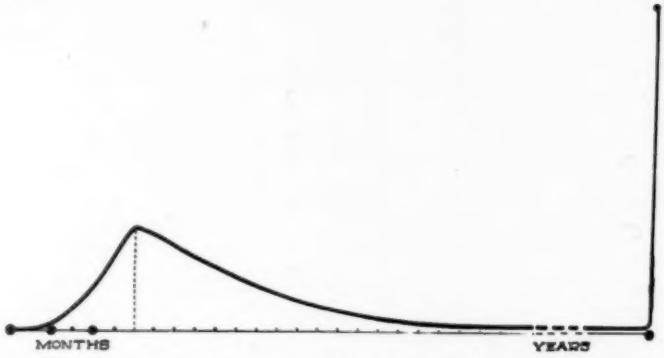


Fig. 1.—The rise and fall of tetanus antitoxin in the serum after three injections of alum toxoid and after a "recall" injection of toxoid given years later.

Our plan originally called for a span of two months between the first and third injections, with an interval of two months before taking the blood specimen. Owing to individual variability in clinic attendance, this plan was frequently not followed. Therefore we have divided our data so as to deal with two variables. The first variable is the elapsed time between the first and last injections; the second is the interval between the last injection and the taking of the blood sample. Antitoxin was tested for at levels of 0.01, 0.03, 0.1, 0.3, 1, 3, 10, and 30 units per cubic centimeter of serum and was usually found to lie between two of the values tested for rather than exactly at any of them (Fig. 2).

It should be emphasized that with neither active nor passive immunization is there a generally accepted level of serum antitoxin below which tetanus may occur and above which it is known not to occur. If we are permitted to draw an analogy with active diphtheria prophylaxis, very small antitoxin levels may suffice to protect against the usual type of infection. Bergey, Brown, and Etris[3] are of the opinion that $\frac{1}{100}$ of a unit of tetanus antitoxin per cubic centimeter of serum may be a minimum protective level. Cowles[4] feels, and we are inclined to agree, that the protective level varies with the amount of toxin produced by the infection, and that in general it seems better to place it at $\frac{1}{10}$ of a

unit per cubic centimeter. It is true, furthermore, that serum antitoxin may not be the sole defense in the immunity mechanism, but it represents that for which we have approximate measurement. It is our feeling, in any case, that a given unitage developed by active immunity may well be associated with greater protection than the same serum antitoxin level arrived at by passive immunity.

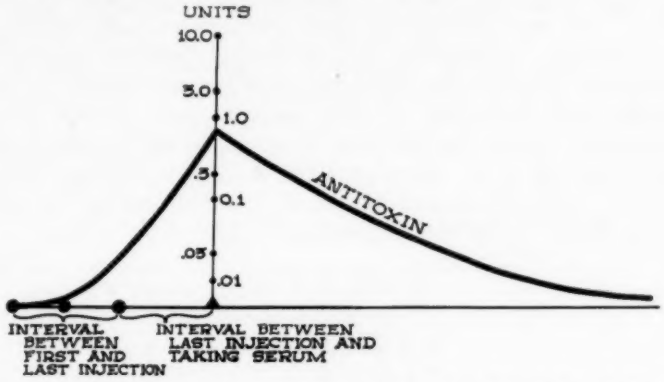


Fig. 2.—Showing the two variable intervals dealt with in this study and the levels at which serum was tested for antitoxin content. The units referred to are American units of tetanus antitoxin.

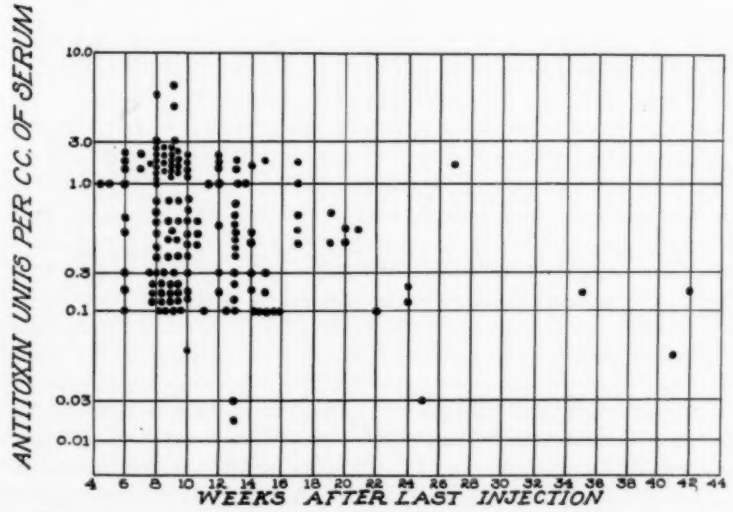


Fig. 3.—The amount of tetanus antitoxin present in 1 c.c. of serum in 156 infants who were given three 1 c.c. injections of combined diphtheria and tetanus alum toxoid. The interval between injections was four or five weeks, and the total interval was eight or nine weeks. Serum was taken at intervals of from six to forty-two weeks after the last injection. All infants were over 7 months and under 12 months of age at the time of the first injection. The dots lying between two lines represent undetermined values somewhere between the level represented by the lower line and that represented by the upper line.

Fig. 3 represents 156 cases in which the immunization was completed within eight or nine weeks, and the variable is the time elapsed between the last injection and the taking of the blood sample. It shows the great variation in response, more than a hundredfold, to a uniform procedure. It is also seen that five infants had levels between $\frac{1}{10}$ and $\frac{1}{100}$ of a unit at the time their serum was taken. Two of the five (Cases 4 and 24 of Table II A) were studied again, six and nine months later than is indicated in Fig. 3, and were found to have moved into the next highest bracket without additional stimulation. Apparently, they formed antitoxin slowly after the initial injections. All these values are lower than we expect will be attained after the recall injection. From previous reports it was expected that in most instances the peak response would occur about eight to ten weeks after the last injection. That such was likely the case in our group is suggested by finding that the five highest values obtained were in blood taken at this time.

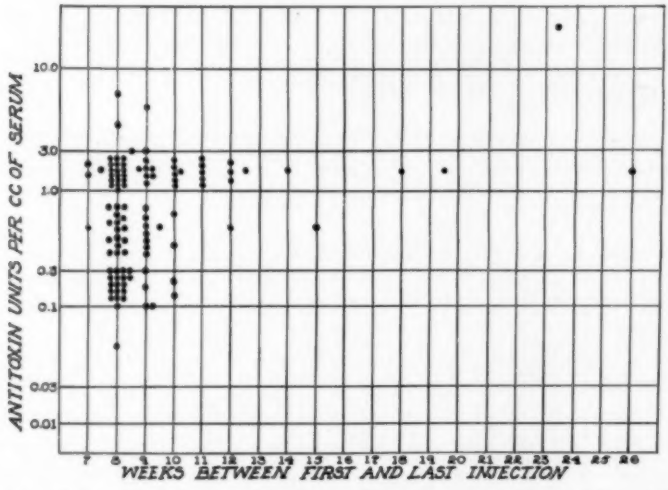


Fig. 4.—Tetanus antitoxin levels in 108 infants whose serum was taken eight to ten weeks after the last of three doses of combined alum toxoid. The interval between the first and the last injection varied from seven to twenty-six weeks. The dots lying between the two lines represent undetermined values somewhere between the level represented by the lower line and that represented by the upper line.

If we consider only the cases in which the blood was taken at this interval of eight to ten weeks after the last injection, we have 108 cases. They are represented by Fig. 4. Here the variable is the interval between the first and last injections. We see that where this interval exceeded ten weeks, higher levels were obtained more consistently than where the interval was less than ten weeks. When this improved response with the longer interval became apparent, it was decided to increase the interval between injections. Since the visits of the infants to the Well-Baby Clinic are made monthly, we now give the three

prophylactic injections on alternate visits, begining at 7 or 8 months of age. This gives an interval of at least four months between the first and last injections.

Tables II A and II B include all cases receiving three injections of the combined alum diphtheria and tetanus toxoids. Table II A includes all those cases represented in Fig. 3 and 4, while Table II B includes those in which either the time intervals or the amounts of antigen were such that they could not be included in Figs. 3 and 4.

Table III lists all patients receiving two injections of 1 c.c. each instead of three. Their number is too few to permit a comparison with those receiving three injections. In a field where over a hundredfold variation is obtained following a uniform procedure, a much larger group is required before a comparison is permitted, and then modes rather than arithmetical averages should be the basis of the comparison.

The initial response, which is the subject of the present communication, is of interest for several reasons. It may be that some relationship between a poor initial response and the recall response obtained years later will be found; however, none is indicated in the studies reported to date. These show that an adequate recall response can be expected in spite of a poor initial response. Furthermore, we have found, as have Bigler and Werner[5] and others, that the individuals who subsequently have a positive Schick test have not necessarily had a poor tetanus antitoxin response. Finally, the initial response is of interest because it deals with a period of probable protection prior to any recall injection. That this period of probable protection may last many months is suggested by the experience of the British Expeditionary Force prior to Dunkirk, where the severe fighting provided a good test of the efficacy of active immunization.[6, 7] A large proportion of the casualties arrived in England five or six days after being wounded and without toxoid or antitoxin therapy. Only 10 per cent of the men had not been immunized, the others having had their initial toxoid up to two years previously. There were eight cases of tetanus in the unimmunized group, while no cases of tetanus occurred among the immunized, a group nine times as large. So far, only one failure of protection of an immunized individual has come to our attention.[8] This is the instance of a French soldier who developed mild tetanus and recovered. He had had the routine nonalum toxoid used by the French army. The insufficiency of a single dose of toxoid, moreover, is illustrated by Jeffrey's[9] report of four cases of tetanus in British soldiers, all of whom had had a single injection of nonalum toxoid and two of whom had also had 3,000 units of antitoxin within six hours of injury.

We cannot refrain from commenting at this point on the interesting question of whether a tetanus infection may not itself act as a recall stimulus just as an additional dose of toxoid would. There are only a

TABLE II A

THREE INJECTIONS OF 1 C.C. EACH OF COMBINED DIPHTHERIA AND TETANUS ALUM TOXOID

| NO. | INTERVAL BETWEEN FIRST AND THIRD DOSES (WK.) | ELAPSED TIME BEFORE SERUM TAKEN (WK.) | TITER (UNITS OF TETANUS ANTITOXIN PER C.C. OF SERUM) | NO. | INTERVAL BETWEEN FIRST AND THIRD DOSES (WK.) | ELAPSED TIME BEFORE SERUM TAKEN (WK.) | TITER (UNITS OF TETANUS ANTITOXIN PER C.C. OF SERUM) |
|---|---|---|---|---|---|---|---|
| 2 | 9 | 24 | >0.1 <0.3 | 140 | 11 | 10 | >1.0 <3.0 |
| 4 | 9 | 12 | >0.01 <0.03 | 141 | 8 | 7 | >1.0 <3.0 |
| | | 41 | >0.03 <0.01 | 143 | 8 | 8 | >1.0 <3.0 |
| 8 | 9 | 13 | >0.1 <0.3 | 144 | 23 (4-19) | 10 | >10.0 <30.0 |
| 10 | 10 | 13 | >0.1 <0.3 | 145* | 8 | 8 | >1.0 <3.0 |
| | | 19 | 0.1 | 146* | 10 | 10 | >0.1 <0.3 |
| 23 | 9 | 17 | 1.0 | 148 | 8 | 8 | >0.1 <0.3 |
| 24 | 8 | 25 | 0.03 | 151 | 8 | 9 | >1.0 <3.0 |
| | | 63 | >0.03 <0.1 | 152 | 8 | 14 | >1.0 <3.0 |
| 25 | 8 | 13 | 1.0 | 154 | 12 (7-5) | 8 | >1.0 <3.0 |
| 27 | 9 | 8 | >0.3 <1.0 | 156 | 9 | 8 | >1.0 <3.0 |
| 43 | 8 | 19 | >0.3 <1.0 | 159 | 9 | 9 | 0.1 |
| 46 | 9 | 6 | >1.0 <3.0 | 161 | 9 | 15 | 0.1 |
| 48 | 8 | 6 | >0.3 <1.0 | 163 | 8 | 9 | >0.1 <0.3 |
| 49 | 9 | 19 | >0.3 <1.0 | 166 | 10 | 9 | >1.0 <3.0 |
| 51 | 8 | 17 | >0.3 <1.0 | 170 | 8 | 12 | >1.0 <3.0 |
| 52 | 9 | 6 | 1.0 | 178 | 9 | 27 | >1.0 <3.0 |
| 55 | 8 | 24 | >0.1 <0.3 | 179 | 8 | 13 | >0.1 <0.3 |
| 56 | 8 | 9 | >1.0 <3.0 | 182 | 8 | 12 | >0.1 <0.3 |
| 60 | 8 | 6 | >1.0 <3.0 | 183 | 9 | 35 | >0.1 <0.3 |
| 61 | 8 | 6 | >1.0 <3.0 | 188 | 9 | 9 | >1.0 <3.0 |
| 69 | 8 | 6 | 0.3 | 195 | 26 (18-8) | 10 | >1.0 <3.0 |
| 70 | 8 | 8 | >1.0 <3.0 | 196 | 8 | 11 | 0.1 |
| 74 | 8 | 6 | >0.3 <1.0 | 200 | 8 | 9 | >1.0 <3.0 |
| 75 | 11 | 8 | >1.0 <3.0 | 201 | 8 | 9 | >0.1 <0.3 |
| 76 | 7 | 8 | >1.0 <3.0 | 202 | 8 | 9 | >1.0 <3.0 |
| 82 | 11 | 9 | >1.0 <3.0 | 203 | 8 | 9 | >0.1 <0.3 |
| 85 | 8 | 10 | >1.0 <3.0 | 205 | 8 | 9 | >1.0 <3.0 |
| 86 | 8 | 8 | >0.3 <1.0 | 208 | 8 | 8 | 0.3 |
| 89 | 8 | 8 | 3.0 | 209 | 8 | 8 | >0.1 <0.3 |
| 95 | 8 | 9 | >1.0 <3.0 | 214 | 8 | 9 | >0.1 <0.3 |
| 97 | 8 | 9 | >1.0 <3.0 | 215 | 9 | 9 | >3.0 <10.0 |
| 98 | 8 | 8 | >0.1 <0.3 | 216 | 9 | 8 | 0.3 |
| 100 | 8 | 8 | >1.0 <3.0 | 217 | 8 | 8 | 1.0 |
| 101 | 8 | 6 | >0.1 <0.3 | 223 | 12 (4-8) | 8 | >1.0 <3.0 |
| 102 | 8 | 8 | >1.0 <3.0 | 228 | 8 | 8 | >0.1 <0.3 |
| 103 | 8 | 8 | >0.3 <1.0 | 229 | 18 (14-4) | 8 | >1.0 <3.0 |
| 104 | 10 | 8 | >1.0 <3.0 | 232 | 9 | 17 | >0.3 <1.0 |
| 106 | 9 | 10 | >0.3 <1.0 | 236 | 8 | 17 | >1.0 <3.0 |
| 107 | 9 | 42 | >0.1 <0.3 | 238 | 8 | 10 | >0.3 <1.0 |
| 109 | 46 (41-5) | 9 | >1.0 <3.0 | 239 | 8 | 9 | 0.3 |
| 110 | 8 | 8 | >0.1 <0.3 | 240 | 9 | 9 | 3.0 |
| 115 | 8 | 9 | >0.3 <1.0 | 241 | 19 (15-4) | 10 | >1.0 <3.0 |
| 116 | 8 | 6 | 0.1 | 244 | 10 | 9 | >0.1 <0.3 |
| 118 | 9 | 10 | >1.0 <3.0 | 245 | 8 | 10 | >0.3 <1.0 |
| 120 | 8 | 15 | >0.1 <0.3 | 248 | 8 | 8 | >0.3 <1.0 |
| 122* | 8 | 9 | >1.0 <3.0 | 250 | 8 | 8 | 0.3 |
| 123 | 9 | 15 | >1.0 <3.0 | 251 | 8 | 9 | >0.3 <1.0 |
| 124 | 8 | 10 | >0.1 <0.3 | 252 | 8 | 13 | >1.0 <3.0 |
| 127 | 8 | 9 | >1.0 <3.0 | 253 | 12 (4-8) | 8 | >1.0 <3.0 |
| 129 | 8 | 12 | >1.0 <3.0 | 254 | 8 | 8 | >3.0 <10.0 |
| 133 | 7 | 9 | >1.0 <3.0 | 255 | 8 | 9 | >1.0 <3.0 |
| 134 | 8 | 9 | >1.0 <3.0 | 257 | 10 | 10 | >0.3 <1.0 |
| 135* | 8 | 8 | >1.0 <3.0 | 258 | 8 | 8 | >0.3 <1.0 |
| 139 | 8 | 7 | >1.0 <3.0 | 259 | 11 | 8 | >1.0 <3.0 |

> indicates "more than"; < indicates "less than."

*The Schick test was positive in Cases 122, 135, 145, 146, 292, and 320 at the time tetanus antitoxin was determined. Of the remaining cases, 10 per cent were not reported and the rest were negative.

TABLE II A—CONT'D

| NO. | INTERVAL BETWEEN FIRST AND THIRD DOSES (WK.) | ELAPSED TIME BEFORE SERUM TAKEN (WK.) | TITER (UNITS OF TETANUS ANTITOXIN PER C.C. OF SERUM) | | NO. | INTERVAL BETWEEN FIRST AND THIRD DOSES (WK.) | ELAPSED TIME BEFORE SERUM TAKEN (WK.) | TITER (UNITS OF TETANUS ANTITOXIN PER C.C. OF SERUM) | |
|---|---|---|---|---|---|---|---|---|---|
| 260 | 8 | 8 | >1.0 | <3.0 | 353 | 14 (10-4) | 9 | >1.0 | <3.0 |
| 264 | 9 | 5 | 1.0 | | 356 | 9 | 12 | >1.0 | <3.0 |
| 265 | 9 | 8 | >1.0 | <3.0 | 357A | 12 (8-4) | 10 | >0.3 | <1.0 |
| 266 | 11 | 9 | >1.0 | <3.0 | 359 | 9 | 10 | >0.3 | <1.0 |
| 267 | 8 | 10 | >0.3 | <1.0 | 360 | 9 | 10 | >0.1 | <0.3 |
| 270 | 8 | 9 | >3.0 | <10.0 | 364 | 10 | 9 | >1.0 | <3.0 |
| 276 | 8 | 9 | >0.3 | <1.0 | 368 | 15 (4-11) | 9 | >0.3 | <1.0 |
| 277 | 8 | 12 | >0.3 | <1.0 | 369 | 9 | 17 | >0.3 | <1.0 |
| 283 | 9 | 21 | >0.3 | <1.0 | 377 | 8 | 10 | 0.3 | |
| 289 | 10 | 9 | >1.0 | <3.0 | 389 | 9 | 14 | >0.1 | <0.3 |
| 290 | 10 | 9 | >1.0 | <3.0 | 390 | 9 | 13 | >0.3 | <1.0 |
| 291 | 9 | 9 | >0.3 | <1.0 | 391 | 9 | 12 | 0.3 | |
| 296 | 8 | 9 | >0.1 | <0.3 | 392 | 9 | 22 | 0.1 | |
| 297 | 8 | 9 | >0.1 | <0.3 | 404 | 9 | 13 | >0.3 | <1.0 |
| 299 | 8 | 10 | >0.3 | <1.0 | 410 | 8 | 13 | >0.3 | <1.0 |
| 300 | 8 | 20 | >0.3 | <1.0 | 413 | 9 | 13 | >0.3 | <1.0 |
| 301 | 10 | 9 | >0.3 | <1.0 | 415 | 8 | 13 | >0.3 | <1.0 |
| 303 | 8 | 8 | >0.3 | <1.0 | 418 | 8 | 13 | 1.0 | |
| 308 | 8 | 9 | >0.3 | <1.0 | 419 | 9 | 12 | 1.0 | |
| 309 | 8 | 8 | >0.3 | <1.0 | 426 | 8 | 20 | >0.3 | <1.0 |
| 310 | 8 | 8 | >0.1 | <0.3 | 430 | 8 | 9 | >0.3 | <1.0 |
| 320* | 9 | 10 | >1.0 | <3.0 | 435 | 9 | 13 | >0.3 | <1.0 |
| 322 | 9 | 10 | >0.3 | <1.0 | 440 | 9 | 15 | 0.3 | |
| 324 | 8 | 10 | >0.1 | <0.3 | 442 | 9 | 14 | >0.3 | <1.0 |
| 327 | 8 | 9 | 0.1 | | 447 | 8 | 13 | >0.3 | <1.0 |
| 329 | 10 | 9 | >1.0 | <3.0 | 448 | 8 | 15 | 0.1 | |
| 330 | 8 | 9 | >0.3 | <1.0 | 453 | 9 | 13 | 0.1 | |
| 335 | 10 | 57 | >0.3 | <1.0 | 458 | 8 | 14 | 0.3 | |
| 340 | 8 | 10 | >0.03 | <0.1 | 462 | 8 | 15 | 0.1 | |
| 341 | 9 | 9 | 0.1 | | 463 | 8 | 13 | 0.3 | |
| 343 | 9 | 10 | >0.3 | <1.0 | 475 | 8 | 13 | >1.0 | <3.0 |
| 346 | 10 | 16 | >0.3 | <1.0 | 500 | 9 | 13 | 0.03 | |
| 348 | 8 | 9 | >0.3 | <1.0 | 524 | 8 | 5 | 1.0 | |
| 349 | 9 | 10 | >1.0 | <3.0 | 554 | 8 | 15 | 0.1 | |
| 350 | 8 | 14 | >0.3 | <1.0 | 582 | 8 | 15 | 0.1 | |
| 351 | 9 | 10 | >0.3 | <1.0 | 583 | 9 | 12 | 1.0 | |
| 352 | 7 | 9 | >0.3 | <1.0 | | | | | |

few experiments which bear on this interesting question, and it cannot as yet be considered settled. Wolters and Dehmel[10] found that two guinea pigs which had been immunized with toxoid seven months previously and whose serum antitoxin level had dropped to 0.02 and 0.05 units per cubic centimeter, respectively, developed an increase of fourfold and thirteenfold amounts of antitoxin within six days of the insertion of a splinter contaminated with tetanus spores and pyogenic organisms. After eighteen days the increase amounted in both instances to over two hundredfold. No symptoms of tetanus appeared. Against this encouraging report on two guinea pigs are the studies of Jones and Jamieson,[11] who found no antitoxin rise in a similar type of experiment in guinea pigs, and also the report of Zuger, Greenwald, and Gerber.[12] These investigators did demonstrate an antitoxin rise in guinea pigs eight to ten days after spores were injected but obtained no consistent evidence that the clinical course was thereby affected.

TABLE II B

THREE INJECTIONS OF 1 C.C. EACH OF COMBINED DIPHTHERIA AND TETANUS ALUM TOXOID

| NO. | INTERVAL BETWEEN FIRST AND THIRD DOSES (WK.) | ELAPSED TIME BEFORE SERUM TAKEN (WK.) | TITER (UNITS OF TETANUS ANTITOXIN PER C.C. OF SERUM) | NO. | INTERVAL BETWEEN FIRST AND THIRD DOSES (WK.) | ELAPSED TIME BEFORE SERUM TAKEN (WK.) | TITER (UNITS OF TETANUS ANTITOXIN PER C.C. OF SERUM) |
|---|---|---|---|---|---|---|---|
| 9 | 36 (31-5) | 11 | >1.0 <3.0 | 374 | 11 | 7 | >1.0 <3.0 |
| 10 | 10 | {13 | >0.1 <0.3 | 383 | 10 | 13 | >0.3 <1.0 |
| | | {17 | 0.1 | 394 | 10 | 13 | >0.3 <1.0 |
| 26 | 10 | 6 | >1.0 <3.0 | 406 | 15 (11-4) | 16 | >0.3 <1.0 |
| 63 | 13 | 21 | >0.1 <0.3 | 408 | 10 | 14 | 0.3 |
| 84 | 11 | 12 | >1.0 <3.0 | 409 | 10 | 14 | >0.3 <1.0 |
| 108 | 13 (6-7) | 7 | >1.0 <3.0 | 417 | 15 (11-4) | 11 | 1.0 |
| 117 | 11 | {21 | >1.0 <3.0 | 420 | 12 (6-6) | 13 | 0.3 |
| | | {56 | >0.1 <0.3 | 422 | 14 (7-7) | 14 | >0.3 <1.0 |
| 126 | 12 (5-7) | 11 | >1.0 <3.0 | 424 | 10 | 13 | >0.3 <1.0 |
| 138 | 10 | 14 | >1.0 <3.0 | 428 | 10 | 18 | >0.3 <1.0 |
| 191 | 13 (5-8) | 13 | >0.3 <1.0 | 443 | 10 | 14 | 0.3 |
| 231 | 11 | 11 | >3.0 <10.0 | 444 | 12 (5-7) | 13 | 1.0 |
| 278 | 10 | 11 | >0.3 <1.0 | 452 | 12 (5-7) | 14 | 0.1 |
| 281 | 12 (6-6) | 14 | >1.0 <3.0 | 460 | 12 | 13 | 1.0 |
| 292* | 33 (17-16) | 23 | >1.0 <3.0 | 469 | 11 | 13 | >0.3 <1.0 |
| 314 | 11 | 11 | >0.3 <1.0 | 477 | 13 (4-9) | 11 | >0.3 <1.0 |
| 321 | 16 (5-11) | 14 | 1.0 | 486 | 11 | 22 | 0.1 |
| 328 | 12 (6-6) | 18 | >0.3 <1.0 | 508 | 10 | 14 | >0.03 <0.1 |
| 357B | 19 (6-13) | 20 | >0.1 <0.3 | 509 | 10 | 13 | 0.03 |
| 363 | 11 | 15 | >1.0 <3.0 | | | | |

*See footnote on p. 176.

TABLE III

TWO INJECTIONS OF 1 C.C. EACH OF COMBINED DIPHTHERIA AND TETANUS ALUM TOXOID

| CASE NO. | INTERVAL BETWEEN FIRST AND SECOND DOSES WK. | ELAPSED TIME BEFORE SERUM TAKEN WK. | TITER (UNITS OF TETANUS ANTITOXIN PER C.C. OF SERUM) | CASE NO. | INTERVAL BETWEEN FIRST AND SECOND DOSES WK. | ELAPSED TIME BEFORE SERUM TAKEN WK. | TITER (UNITS OF TETANUS ANTITOXIN PER C.C. OF SERUM) |
|---|---|---|---|---|---|---|---|
| 12 | 37 | 5 | >3.0 <10.0 | 187 | 24 | 23 | >0.03 <0.1 |
| 41 | 36 | 40 | >1.0 <3.0 | 204 | 4 | 11 | >0.1 <0.3 |
| 78 | 4 | 10 | >3.0 <10.0 | 212 | 5 | 29 | >0.3 <1.0 |
| 90 | 4 | 13 | >1.0 <3.0 | 242 | 5 | 41 | >0.1 <0.3 |
| 96 | 4 | 19 | >0.1 <0.3 | 243 | 4 | 9 | >0.1 <0.3 |
| 119 | 4 | 22 | >0.1 <0.3 | 246 | 17 | 21 | >0.3 <1.0 |
| 131 | 10 | 7 | >0.1 <0.3 | 285 | 12 | 31 | >0.3 <1.0 |
| 137 | 16 | 20 | >1.0 <3.0 | 371 | 4 | 5 | >0.3 <1.0 |
| 175 | 5 | 22 | >0.1 <0.3 | 388 | 4 | 27 | >0.03 <0.1 |
| 176 | 5 | 22 | >0.1 <0.3 | 438 | 4 | 16 | 0.3 |
| 185 | 6 | 18 | >0.3 <1.0 | 449 | 6 | 11 | >0.3 <1.0 |

One other report can be considered to bear on this subject. Cowles[4] mentions the case of a man who years previously had recovered from a case of tetanus. Upon receiving tetanus toxoid, his response was no different from that of an individual who had had no previous contact with tetanus toxoid, or with the presumably antigenically identical tetanus toxin.

In our infants local reactions occurred but were not troublesome. In general they were comparable to those of Sauer's pertussis vaccine. Induration and tenderness occasionally occurred over an area 1 to 3 cm. in diameter, and in some instances compressing was advised, although this was unusual. In such instances the tenderness was usually slight and less than that associated with pertussis vaccine, although redness and induration tended to last a few days longer. As is to be expected with an alum product, a subcutaneous nontender nodule persisted at the site of injection for as long as a month, and sometimes for two or three months. No abscess formation occurred in over 1,500 injections in infants. While the number of older children injected was much fewer, we received a definite impression that they were much more likely to have induration and tenderness than the infants. Two girls of 7 years of age developed small sterile abscesses. Strangely enough, these girls were identical twins. We believe alum toxoid should be injected deeply, subcutaneously or intramuscularly, and the area massaged thoroughly after injection.

General reactions were noteworthy for their absence. In two instances mild urticaria occurred an hour or two after an injection, and in one instance a mild asthmatic attack occurred within four hours of an injection. In none of these instances were the other injections of the series followed by similar symptoms. In all three the symptoms referred to had also occurred prior to any injection.

As previously stated, Schick tests were made at the time serum was taken. Ninety-six per cent negative reactions were obtained in a follow-up which included 90 per cent of the cases. Those with positive Schick tests did not have particularly low tetanus antitoxin values, as can be seen in Tables II A, II B, and IV.

In the course of preparing this report for publication, that of Bigler and Werner[5] appeared. It deals with children as well as infants and further differs from our report in the following:

1. The usual interval between injections was three months rather than one month.

2. Mice rather than guinea pigs were used in tetanus antitoxin assays.

3. Diphtheria antitoxin determinations were made rather than Schick tests.

4. What we regard as the third injection of the basic immunity is considered by these authors as a stimulating or recall injection.

The same type of combined diphtheria and tetanus alum toxoid was used in both studies save in some of the third injections of Bigler and Werner, where tetanus alum toxoid was used.

The results of these authors show higher levels than were obtained in our infants. Whereas we assumed the height of the initial response

occurred in the neighborhood of two months after the third injection, Bigler and Werner imply they found it one week after two injections, or two weeks after three injections. They compare the average values of groups of a few cases each in support of this conclusion. A recalculation of their data, however, shows that such is probably not the case. When the ninety-seven cases in Tables I and II in their report are combined, the average is higher at one month than at any other time. That the evidence of such averages is not valid, however, is illustrated by an examination of their reported average of 3.52 units one week after the second injection. This is derived from five cases, the lowest of which is 0.1 unit and the highest of which is 10 units. Omission of the latter case causes the average to drop to 1.9 units. Elsewhere in the report it appears that there is a failure to develop a significantly higher level one week after the third injection (average 3.65) than was obtained a week after the second injection (average 3.52). The explanation probably is that with such wide variations the average of a few cases can be misleading. The mode of a sufficient number of cases would be more informative. The value of 3.65 units on the seventh day after the third injection, for example, drops to 2.65 if Case 35 with a value of 35 units per cubic centimeter of serum is omitted.

TABLE IV

INJECTIONS AS INDICATED OF COMBINED DIPHTHERIA AND TETANUS ALUM TOXOID

| NO. | INTERVAL BETWEEN FIRST AND LAST INJECTIONS WK. | ELAPSED TIME BEFORE SERUM TAKEN WK. | TITER | COMMENTS |
|---|---|---|---|---|
| 87 | 5 | 6 | 0.03 | 3 injections; total dose, 1.0 c.c. |
| 153 | 7 | 9 | >0.1 <0.3 | 3 injections; total dose, 2.0 c.c. |
| 167* | 8 | 9 | >0.3 <1.0 | 3 injections; total dose, 2.4 c.c. |
| 13 | 8 | 15 | 0.1 | 3 injections; total dose, 2.5 c.c. |
| 5 | 4 | 22 | >0.1 <0.3 | 2 injections; total dose, 1.0 c.c. |
| 11* | 4 | 31 | >0.3 <1.0 | 2 injections; total dose, 1.5 c.c. |
| 19 | 4 | 31 | >0.1 <0.3 | 2 injections; total dose, 1.5 c.c. |
| 20 | 4 | 38 | >0.03 <0.1 | 2 injections; total dose, 1.5 c.c. |
| 193* | 4 | 8 | >0.1 <0.3 | 2 injections; total dose, 1.6 c.c. |

*Positive Schick tests.

Bigler and Werner refer to the third injection as the stimulating injection. As well over half of these third injections were given within three months of the second injection, it seems to us they should be considered more correctly as part of the primary immunization. The term "stimulating injection" we feel would better be applied to injections given a year or more later.

We are in agreement with these authors that a long interval between injections is desirable. Our present plan of a two months' interval, however, was chosen with an eye also to completing three injections while

most of the infants were still under routine Well-Baby Clinic supervision. We feel that it remains to be shown whether three injections are significantly superior to two injections. So far with three injections we have not encountered a failure of antitoxin response comparable to that reported by Bigler and Werner in one instance after two injections (Case 23, Table I). Both reports are inconclusive so far as the results of late recall injection are concerned. This phase of the problem is, of course, of the greatest importance in order to assure the status of toxoid in preference to the present routine use of antitoxin. We plan to continue our studies and to report further on this phase of the study.

## SUMMARY

Over 600 infants have been given combined diphtheria and tetanus alum toxoid. The majority received three injections at intervals of one month each. Where the interval was longer, however, a higher tetanus antitoxin response tended to occur. The variation in tetanus antitoxin response was very great, but all of the 240 cases in which it was determined had over $\frac{1}{100}$ of a unit of antitoxin following this primary immunization procedure. Ninety-six per cent negative Schick tests were obtained. The infants tolerated the antigen well. A study of their response to a late "recall" injection of tetanus toxoid is in progress.

The Cutter Laboratory, Berkeley, kindly aided us in establishing our technique in guinea pig assays and determined the titers in the early portion of this study.

The combined diphtheria and tetanus alum toxoid used in this study was supplied through the courtesy of Eli Lilly and Co.

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# THE DIFFUSION OF SULFATHIAZOLE INTO AND FROM THE PERITONEUM

## A Case of Pneumococcus Peritonitis Treated With Sulfathiazole Orally and Intraperitoneally

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THERE is little mention in the literature of the diffusion of sulfathiazole into and from the peritoneum. This factor is of great significance in treating a bacterial peritonitis with this drug. If sulfathiazole administered orally should not find its way into the peritoneum in sufficiently high concentrations, this route would be useless.

The only pertinent report is by Sadusk, Jr., and his co-workers[1] who have demonstrated in cases of ascites due to cirrhosis of the liver that oral sulfathiazole does diffuse readily into the ascitic fluid.

Our patient entered the hospital with a nephrotic type of nephritis. During his stay in the hospital he developed a pneumococcus peritonitis. The peritonitis was treated with sulfathiazole. This was administered at first orally and later intraperitoneally. The blood and peritoneal fluid sulfathiazole levels were compared frequently throughout the period of therapy.

F. J., a 7-year-old colored male was admitted to Metropolitan Hospital on Dec. 18, 1940, because of "swelling of the face and scalp, and dark cloudy urine."

Family and past histories were noncontributory.

*Present Incident.*—During the month prior to hospitalization the child had several mild upper respiratory infections. The swelling of the face and scalp and dark urine were noted four days before admission.

The positive physical findings on admission were edema of the face and scalp, a mucopurulent nasal discharge, slightly injected pharynx, postauricular nodes (left), many small cervical and axillary nodes with a few larger ones in the left axilla, an inconstant short systolic over the apex of the heart, and a blood pressure of 124/80.

*Laboratory Data.—Urine analysis:* 4 plus albumin, many granular and waxy casts and red blood cells; the P.S.P. test was 25 per cent in two hours. *Blood count:* R.B.C., 2,800,000; Hb., 62 per cent; W.B.C., 16,500; 73 polymorphonuclears, 27 lymphocytes. *Sedimentation rate,* 21 in 15 minutes; 72 in one hour. *Blood chemistry:* Cholesterol, 390 total, 156 free, 234 esters; N.P.N., 55; serum proteins, 4.59 total, 1.67 albumin, 3.08 globulin, 0.84 fibrinogen.

Mantoux, Vollmer, Wassermann, and Paul-Bunnell tests were negative.

A diagnosis of a nephrotic type of nephritis was made.

*Course.*—The urinary output was low in spite of all attempts to increase kidney secretion. The abnormal blood and urinary findings persisted during the entire stay in the hospital. Ascites first appeared on Dec. 26, 1940, and increased so rap-

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idly that it was necessary to do an abdominal paracentesis every three weeks. The child's weight was 53¾ pounds on admission and had increased to 81½ pounds by Jan. 14, 1941.

On May 4, 1941, the temperature rose to 104° F., the respiratory rate was 40, and the child appeared toxic. X-ray established a diagnosis of right lower lobe pneumonia. The pharyngeal swab, blood culture, and abdominal cultures all showed a type VI pneumococcus. One hundred thousand units of specific serum were given, and within twelve hours the temperature and respiratory rate returned sharply to normal.

However, on May 8, the temperature once again rose to 103°, but the respiratory rate remained normal, and there was generalized abdominal pain and tenderness. The clinical impression was that the pneumonic process had subsided and the elevated temperature and symptoms were due to the pneumococcic peritonitis. Sulfathiazole therapy was instituted. A daily dose of 0.2 Gm. per kilogram (1½ gr. per pound) of approximately true body weight was given orally. The following day the temperature returned to normal. From May 10 to May 16 the sulfathiazole dosage was 0.1 Gm. per kilogram (¾ gr. per pound). The blood and peritoneal fluid sulfathiazole levels were compared, and cultures of the peritoneal fluid were done during the period of therapy (Table I).

TABLE I

| DATE | BLOOD SULFATHIAZOLE | | | PERITONEAL FLUID SULFATHIAZOLE | | | PERITONEAL CULTURE |
|---|---|---|---|---|---|---|---|
| | TOTAL | FREE | CONJ. | TOTAL | FREE | CONJ. | |
| 5/ 5 | | | | | | | Positive |
| 5/15 | 6.27 | 3.93 | 2.34 | 5.03 | 3.00 | 2.03 | Positive |
| 5/16 | 8.16 | 4.81 | 3.35 | 7.01 | 4.00 | 3.01 | Positive |
| 5/19 | 2.38 | 1.09 | 1.29 | 2.38 | 1.16 | 1.22 | Negative |
| 6/ 4 | | | | Trace | Faint trace | | Negative |
| 6/ 9 | | | | | | | Negative |

Orally administered 0.2 Gm. per kilogram (1½ gr. per pound), 5/8/41 to 5/10/41; 0.1 Gm. per kilogram (¾ gr. per pound), 5/10/41 to 5/16/41.

Locally administered 80 c.c. of 5 per cent sodium sulfathiazole on 5/16/41 after the determinations of blood and peritoneal fluid sulfathiazole levels were done.

On May 15, although the patient was afebrile and symptom-free and had a total concentration of 5.03 mg. per 100 c.c. of sulfathiazole in the peritoneal fluid, culture of this fluid remained positive for pneumococci. On May 16 with a total concentration of sulfathiazole in the peritoneal fluid of 7.01 mg. per 100 c.c. the culture still was positive. Oral administration of the drug was discontinued and 80 c.c. of 5 per cent sodium sulfathiazole (4 Gm.) were injected directly into the peritoneum. The next peritoneal fluid culture on May 19 was negative, although the drug concentration in the fluid had fallen to 2.30 mg. per 100 c.c. Cultures on June 4 and June 9 were also negative.

## COMMENT

This boy had a markedly diminished kidney function. Sulfathiazole was selected in preference to sulfapyridine because of the lower incidence of toxic reactions, especially those involving the kidneys. No untoward effects were noted during the entire course of therapy.

In Table I the blood and peritoneal fluid sulfathiazole levels are compared. Following oral administration, the peritoneal fluid sulfathiazole level was over 80 per cent of the blood level, which demonstrates the ready diffusibility into the peritoneal fluid.

Although the clinical response to oral sulfathiazole was good, peritoneal fluid cultures on May 15 and May 16 remained positive for pneumococci. Oral administration, which had been started on May 8, was discontinued on May 16, and sodium sulfathiazole was injected intraperitoneally at this time. Subsequent peritoneal cultures were negative for pneumococci. On May 19 blood and peritoneal fluid levels had fallen but were approximately equal. The free sulfathiazole at this time was slightly higher in the peritoneal fluid. On June 4 only a trace was still present in the peritoneal fluid. This indicates that sulfathiazole diffuses from the peritoneum.

The fact that the peritoneal fluid culture became negative for pneumococci only after intraperitoneal administration of sulfathiazole is interesting but not conclusive. It is possible that the transient high concentration of free sulfathiazole following the instillation was sufficient to sterilize the peritoneal fluid. We shall try to check the efficacy of this route of administration in future cases.

## CONCLUSIONS

1. Sulfathiazole diffuses readily into and from the peritoneum.
2. A patient with pneumococcus peritonitis responded well clinically to oral sulfathiazole, but the peritoneal fluid became sterile only after intraperitoneal instillation.

## REFERENCE

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# SULFATHIAZOLE IN THE TREATMENT OF PNEUMOCOCCIC PNEUMONIA IN INFANTS

## A Brief Note on the Development of Pneumococcic Meningitis During Therapy

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COMPARISON of sulfapyridine and sulfathiazole for the treatment of pneumococcic pneumonia in infancy has been made by several investigators and both drugs have been shown to be satisfactory agents. Carey[1] found that sulfathiazole gave less nausea than sulfapyridine, was more effective against the occasional undiagnosed staphylococcic pneumonia, and was a little more rapid in action. We have not differentiated strongly between the two drugs here, although sulfathiazole has gradually become the one of choice among most of the house staff.

Lately we have had the opportunity of observing two cases which lead us to question this policy. The first, a 6-month-old baby, was treated with sulfathiazole for a primary confluent pneumonia of the left upper lobe. He responded nicely to this therapy and the temperature fell to normal by the third day. On the sixth day pyrexia recurred and was accompanied by a generalized convulsion. Lumbar puncture yielded cerebrospinal fluid with an elevated cell count (1,300 cells per cubic millimeter, of which 95 per cent were polymorphonuclear forms), an increased amount of protein, and numerous type XIX pneumococci. It is of extreme interest that the content of sulfathiazole in this specimen was less than 1 mg. per cent, while a blood sample taken simultaneously contained over 7 mg. per cent. This child at autopsy was found to have a diffuse purulent meningitis without evidence of an otitic origin.

The second patient died a few minutes after admission to the hospital and our records are necessarily incomplete. He was 8 months old, had been treated for bilateral confluent pneumonia with sulfathiazole, and apparently had responded well before evidence of central nervous system involvement appeared. A lumbar puncture before hospitalization had shown 550 cells per cubic millimeter and type I pneumococci.

It is generally supposed that sulfathiazole does not readily pass into the normal cerebrospinal fluid, an assumption we have confirmed in several children recently. A cerebrospinal fluid level in excess of 1 mg. per cent is rare, even when the blood level is well within the therapeutic range, and this would seem to hold even when an inflammatory reaction is present in the meninges. Whether the course of these two patients

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would have been different had sulfapyridine been used is entirely in the realm of speculation; certainly, we know, there would have been a bactericidal level of the drug in the cerebrospinal fluid before invasion took place. Meningitis is among the gravest of complications occurring during pneumococcic pneumonia and is certainly no rarity, especially when cases are considered in which involvement of the otitic tract is interposed. Sulfathiazole apparently does not prevent its development, and if sulfapyridine can be shown to do so by virtue of greater diffusion, it would be an attribute more than balancing the slight edge claimed for sulfathiazole on other scores.*

These experiences also lead us to be a little more thorough in our consideration of chemotherapeutic substances for the treatment of aural infections. Our policy includes a careful bacteriologic study and then the selection of a drug, combining effectiveness against the invader with maximum protection to the meninges through an adequate level of the agent in the cerebrospinal fluid.

REFERENCE

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*Comment on sulfadiazine must necessarily be deferred until more data are available in the pediatric literature. From present reports, it would seem to be comparable to sulfapyridine as far as diffusibility is concerned.

# A FIVE-YEAR CLINICAL STUDY OF FACTORS AFFECTING FIRST DENTITION

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THE present analysis is a reversal of the usual method of studying dental caries. Instead of selecting children with and without caries and probing into their pasts for important factors, a group of infants before they had any teeth were chosen for a long-time observational study. During these five or six years pertinent data were recorded. These data were then summarized before the state of caries of the children was finally determined, and the present analysis is based on these data.

## THE SOURCE OF MATERIAL

The Oak Street Health Center from which the material is drawn is ideally organized for such a study. The center was started by the Child Hygiene Committee of the American Association of University Women (A.A.U.W.) for the purpose of educating foster mothers in the care of their infant wards, these women presumably lacking the maternal instinct to care for the young with which the real mother is endowed. The young women in charge, however, soon realized that the foster mothers were getting a type of training that they themselves were not receiving for the care of their own babies. Consequently an educational center was started for the mothers of the city. It may be added that this work was later taken over by private pediatricians and the department of health, leaving the A.A.U.W. to extend and investigate other needs. The present study is one of these investigations.

A lay group of college women superintend the Health Center and give volunteer services at the conferences. A full-time nurse is employed. A group of women physicians and dentists donate their services. A physiotherapist and two psychologists are paid a small fee for their contributions and a near-by teachers' college permits its students to get practical experience at the playground where the children are kept while the mothers are in conference or attending lectures. When these students are not available, volunteers are sought. The object of the Center is to give mothers a well-rounded education in the health supervision of children. The mothers who are registered are not handicapped by extreme poverty and in most instances are intelligent and cooperative. The nurse visits the homes and is familiar with the finances, the general hygiene of the home, crowding, happiness, overwork, conscientiousness of the mother, etc. At present, two well-baby and two preschool conferences are held each week. The babies are graduated into the preschool class at the age of 18 months and after they have been vaccinated, immunized, and Schick tested. In addition to dietary instruction and supervision, special attention is given to dental hygiene, posture, mental hygiene, and social adjustment.

In starting the dental study, the following plan was first outlined. It has been modified to meet altered conditions. Miss Edna Rockstroh, who had been nurse in charge for several years, was asked to select a group of mothers who were intelligent and cooperative and who would probably remain in the city for the

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next several years. These mothers were told that we wished to make a rather long-time observation of the children's teeth and nutrition and that they might be called in from time to time in addition to the regular visits. After this preliminary segregation the mothers were in no way set apart and soon lost track of their "special significance." The mothers and babies came to the regular conferences except for an occasional call when it was necessary to ask them to come in on a special day to get caught up with back examinations. In 1937 Miss Rockstroh's place was taken by Miss Frieda Caffin; although this change was made, the work continued uninterrupted, as both nurses were familiar with the work. The nutritional supervision of the first year, although under two or three different doctors, was the standard routine as discussed later. The dental study group, after selection, has been entirely under the supervision of Dr. H. E. Thelander; the dental inspection has been done largely by Dr. Charlotte Greenhood, but some help in the final check-up was given by Dr. Florence Melkonian.

## INFORMATION OBTAINED

The history of the family, the mother's pregnancy, etc., were taken as soon as the study was started in order to avoid as far as possible the errors which come with lapse of time and consequent forgetfulness as well as the bias that might creep into a history later if teeth were found decayed. The family history included the ages of both parents, the place of birth, nationality, type of work done, health in general, and the condition of the teeth in particular. The pregnancy history included general health, appetite and eating habits, nausea or vomiting, toxemia, prenatal supervision, fortification of diet prenatally with cod-liver oil, calcium, etc. The early history of the infant included such factors as prematurity, birth injury, breast feeding, age at which vitamin D and C and solid foods were added. Special note was made of allergic tendencies and the substitute foods used when allergy was present. Most of the babies had been at the Center from the age of 4 or 5 weeks and the above information became actual record rather than maternal reports. At the first and last examinations anthropometric measurements were made on the children. At all other visits routine examinations were made.

The general feeding advice given at the Center has been that of accepted pediatric practice. Breast feeding was encouraged when possible; often the babies were already on a bottle when enrolled at the clinic. Whole or evaporated milk formulas were used almost exclusively. At times it was necessary to resort to a dried or acid milk and very occasionally soy bean was used for a short period of time. Cod-liver oil or a substitute was given, usually starting at the third or fourth week and continuing throughout the observation period. Sun baths were given when the weather permitted, and if mothers are a little courageous some sun exposure can be had in this locale most of the year. Many of the milk preparations now are either irradiated or have vitamin D added. As a general rule, therefore, only one teaspoonful of cod-liver oil or its equivalent was given a child daily. Vitamin C, usually in the form of orange juice, was stressed. If for any reason it could not be taken,

other fruit juices were substituted, such as tomato, lemon, or grapefruit juice. If none of these were tolerated in adequate amounts, ascorbic acid was given, 25 to 50 mg. daily until an age when raw fruits and vegetables could be taken. Cereal and vegetables were started between 3 and 4 months, fruit at about 5 months, and egg yolk at or near 6 months. Raw fruit and vegetables were added at 16 to 18 months. Special attention was paid to sugars and starches. The sugar of the formula was decreased as cereal and fruits were added and was usually omitted entirely at 6 to 7 months. Between this age and 18 to 20 months the sugar content of the diet was relatively low. As the child grew older and more determined, his own likes and dislikes played a greater role. If he did not like sweets, this with the recommended diet kept the sugar content in his diet relatively low, but if he had a distinct craving for sweets, the amount he received might vary greatly. The conscientious mother might limit his intake effectively but if grandparents were indulgent and the mother casual, his intake would probably be above the desired amount.

The dental examinations were made with a mirror and probe and recorded according to the Bodecker index. Inasmuch as only the extreme, the best, and the worst teeth would be compared, bite-wing plates for hidden caries were not taken. Although x-rays may have changed the index in some of the children, the teeth in the two extreme groups were so obviously different that factors influencing them could still be compared. Some examinations were made of the parents' teeth, but complete studies were difficult to get.

## ANALYSIS OF MATERIAL

In the original group, 105 children were selected. Of these, 11 dropped out early in the study and 16 attended only until the age of 3 or 4 years. Seventy-eight were followed for a long enough period to make an analysis worth while. There were 44 girls and 34 boys in the study. The final tooth analysis was made from the examination at the age nearest 6 years, placing the age for the final examinations between 5 and 6½ years. Some of the children began losing their baby teeth as early as 5 years, and others retained all of them until 6 or 6½ years. These studies did not take into consideration the time of eruption of the teeth or, therefore, the length of time of exposure to dental decay. It was felt that in as small a series as this, such division would subdivide the figures needlessly and complicate the study; furthermore, there would be no advantage gained by so doing, for the large divisions of the groups and limiting of comparisons to the extremes would allow for the variations due to differences in exposure time. The dental studies were kept on a separate sheet and in order to avoid any bias due to advance knowledge of caries, the analysis of all recorded factors for each child was made and placed on his medical record before the dental sheet was analyzed. The information record was made as recorded in Table I.

The importance of these factors to the first dentition is not known, but some of the possible relationships will be mentioned.

The nationality of the parents and whether born here or abroad, although obtained, was not entered in this analysis. Many factors are involved in nationality. Heredity per se may be of significance, but even more important are habits and customs of different countries and the effect of transplantation on these. Food preferences and methods of preparation are often handed on from one generation to another. Greater affluence may be a detriment instead of an asset to migrants. Thus the Scandinavians and the French, who are fond of and experts at preparing pastries, often indulge too heavily in these luxuries when the economical ban to them is removed. The replacement of whole cereals and bread by delicacies results. The change in diets due to migrations and intermarriage could be discussed indefinitely but is only mentioned here as a field for education in health centers and like institutions.

A history of the condition of both the mother's and father's teeth was obtained. In some instances the mother's teeth were also inspected by the dentist; it was impossible or impractical to get the fathers in for such an examination. The status of the parents' teeth may not be exactly accurate but since the groupings are elastic (good, fair, and bad) the extremes are probably quite definitely picked up. Parents in turn naturally would be subject to an equal number of factors pertinent to teeth as are the offspring. The age of the mother may be significant. There is an optimum time for women to bear children; whether or not children born to the older mother may lack some of the essentials to good dental development is not known, but it is a factor that should be noted in this type of observation. Cognizance was also taken of the fact that the chronologic and physiologic ages of women may not be the same; one woman at 40 may be younger physiologically than another at 35. Note was made of signs of premature aging. Frequent pregnancies may drain the mother's reserve to a point where the fetus may also lack essentials for optimum development. The general health of the mother and particularly any endocrine disturbance may be factors in optimal fetal structure. Vomiting, if severe and persistent, may interfere with nutrition; if mild it is probably of little significance. Toxemia was similarly evaluated. The diet during pregnancy was described as "good" if the mother ate well of all the essential foods, such as milk, meat, eggs, fruits, and vegetables. Many in addition had extras, such as cod-liver oil, vitamin C, or calcium. The diet was classified as "bad" if vomiting had interfered for a period of several months, if the mother's tastes had influenced her to eat excessively of some foods to the exclusion of others, or if poverty or place of residence had prevented her from obtaining the right foods. The mothers who ate indifferently or had normally rather poor eating habits were placed in the group "fair."

Notes were made on environmental factors, such as poverty, crowding, and poor hygiene in the home. Under the title "work" was placed not only the mother overworked in the home, but also the mother who had to help support the family by going to work outside the home. When this happens, unless a grandparent is available and willing to assume responsibility for the care of the children, frequent change of helpers and incompetent help is the rule. The children thus cared for are apt to get inadequate care regardless of instructions given.

Mothers vary a great deal in conscientiousness toward their maternal duties. A mother, however, was classed as "casual" only after being under observation for several months, and this characteristic was noted both by the nurse and the physician as of sufficient importance that it might result in bad habits for the child. A certain amount of casualness is an advantage. The overly conscientious mother too frequently creates an attitude in the child of dislike for food and for eating per se, the end result of which is often a child of poorer nutrition than that of the casual mother whose child has a robust appetite and sufficient exposure to good food to select an adequate diet. The general talks, as well as the personal education in mental hygiene at the Center, decreased the problem of the child who is negativistic toward food to a minimum. When the child becomes older, that is 3 or 4 years of age, indulgence in sweets in the form of candy is apt to become a habit unless the mother is at least moderately conscientious about keeping it from the child.

The story of the child himself developed before us with careful notes taken at each visit. There were no premature children in the group. The number of allergic children was remarkably low. Under severe allergy were placed those whose diet or food intake was materially affected by the allergy. Into the group of "slight allergy" were placed those who were reasonably controlled with adequate substitution and the general health was not impaired. Illnesses were classed as "few," "moderate," and "many." These had to be evaluated not only on the basis of numbers, but also on the basis of severity and the type of illness. Two or three minor colds a year is not unusual during the preschool period. If colds were numerous, severe, and one or more other diseases were contracted, especially prolonged ones such as pertussis or scarlet fever, the children were placed in group "many." The rest were classed under "moderate."

The scientist may weigh and properly mix the ingredients of a test tube, but what the pediatrician prescribes and the child actually takes cannot be thus gauged. Even what the mother states he eats and the child's real intake may differ considerably. In an attempt to evaluate the actual intake of the child, an indirect approach was used. On the chart were listed the following foods: milk, meat, eggs, cereals, fruits, vegetables, sweets, cod-liver oil, etc. During the child's visit, however, the discussion was kept informal. His appetite, his likes and dislikes, second helpings, icebox raidings, grandparents' bribes with

sweets, etc., were all covered in an easy chat with the mother and then recorded on the chart. At each visit suggestions and recommendations were made when indicated. There was never any dictation regarding what the child must have or any scoldings for failures to carry out suggestions. I believe I have had the confidence of the mothers and obtained an accurate picture of the children's intake of food. Notes on the chart read like this: "Likes his milk, takes a quart daily." "Dislikes meat and it must be urged." "Likes candy but mother limits amount he gets." Even though poverty figures some in this series, I do not believe that the children were deprived of essential foods; the mothers may have been. A difficulty in evaluating food intake occurred in children who changed from year to year. A child may like and take his milk for 2 or 3 years and then suddenly refuse it and continue doing so for another year or two. By making three groups, "good," "poor," and "fair," such children were placed in the "fair" group and the extremes could be compared.

Breast feeding was classed as "none," "newborn period," and "yes." The reason for this type of division was partly personal. The adjustment of the newborn to his environment is more than the establishment of respiration and circulation. Probably equally fundamental adaptions are those to an unsterile environment, blood production, and endocrine balance. Although the human young in distinction to some other mammalia can survive the establishment of a normal flora without the aid of colostrum, no studies have been made on the effect of colostrum or breast milk on adrenal atrophy or neonatal blood changes. Recent investigations have shown that breast milk is high in vitamin C, a factor entirely or almost absent in artificially prepared formulas. Vitamin C apparently plays a role in dental development and is found in abundance normally in the adrenals. The neonatal period may be rather crucial. In the third group, "yes," were placed all those who were nursed beyond a month.

As mentioned earlier, the dentists recorded caries according to the Bodecker index. In the first dentition there are twenty teeth, each tooth with five surfaces, making a total number of one hundred surfaces. Caries can therefore be expressed directly by percentages, one cavity being 1 per cent. It is the impression of both dentists and pediatricians that a variation in susceptibility to caries ranging from "caries immune" to extreme vulnerability exists and that to some extent this variation is independent of many factors. Some children under the most adverse circumstances continue free from caries while others with the utmost precautions will develop them. Frequency distribution curves for individual variations have been plotted for almost all human characteristics, such as height, weight, width, and even immunity to diphtheria. It seemed desirable to divide this group of children by some such method. To do this was rather difficult, but arranged in order of the number of cavities, there were twenty-seven

children called Group A who on inspection and dental examination, as noted above, had no cavities or the filling of a small fissure only; at the other extreme were eighteen children called Group C with six or more cavities; in between were thirty-three children grouped as B, with varying degrees of caries, between one and five. After this distribution had been made the individual records previously analyzed were checked off as seen in Table I. For comparison in the final table, only the two extreme groups, those with no caries and those with rampant caries, are recorded (Groups A and C). By adding all the adverse factors of each group and dividing by the number of children in that group, the number of adverse factors per child is obtained. In Group A, the noncarious group, the figure is 1.9 per child as compared with 3.66 per child in Group C. In Group B the figure is 2.4 factors per child. After the preliminary study, as will be described later, it was found that in certain of the divisions, such as for instance the child's health, there was no difference in Groups A and C. When the adverse factors of these divisions were omitted from the calculation, the figures changed to one adverse factor per child in Group A to 2.9 in Group C, a ratio of 1:3.

In order to compare separate items, such as mothers' teeth for instance, the adverse factors for these divisions were added across the table and also stated in percentage of the whole, making the figures comparable. The results thus obtained are summarized in Table II and the ratios of Group A to C are given. Some interesting findings may be noted. In Group A 33.3 per cent of the mothers' teeth are bad and 63 per cent are good, while in Group C 66.7 per cent are bad and only 5.6 per cent are good, making a ratio of 1:2 for the bad teeth alone and an astonishing difference if the good teeth of the two groups are compared, 63 to 5.6. In contrast, no such differences appear on the fathers' records. This may indicate that either heredity per se plays no role or that as a single factor it is masked by many other factors involved. It is reasonable to believe that many of the factors influencing the mothers' teeth are still operating and influencing the teeth of the fetus. Maternal factors such as age and health show a ratio of 1:4.5; all adverse factors during pregnancy, 1:2, and the combined environmental factors, 1:9. In contrast to the high correlation found in these factors are the negative correlations in the next divisions. Thus there is no correlation between the children's health in Groups A and C and no correlation for breast feeding or the ordinary constituents of the diet, such as protein, cereals, fruits, and vegetables. There is, however, a positive correlation between the sugar intake and also between the vitamin A and D intake in the two groups. It would appear from these observations that both prenatal and postnatal factors influence the first dentition; that of these factors the prenatal are of greater significance than the postnatal factors. Of the latter, an excess of refined

TABLE I

| | | | CASES | GROUP A 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Familial factors | Mother's teeth | good | | | | | | | | | | | | | | | | | | | | | | |
| | | bad | | | | | + | | + | | + | | | + | + | | | + | | | + | | + | |
| | | fair | | | | | | | | | | | | | | | | | | | | | | |
| | Father's teeth | good | | | | | | | | | | | | | | | | | | | | | | |
| | | bad | | | | | + | | | | + | | | | + | + | | + | + | | + | | + | |
| | | fair | | | | | | | | | | | | | | | | | | | | | | |
| Maternal factors | Mother's age | under 35 | | | | | | | | | | | | | | | | | | | | | | |
| | | over 35 | | | | | + | | | | | | | | | | | | | | | | | |
| | Frequent preg. | yes | | | | | | | | | | | | | | | | | | | | | | |
| | Ill health | yes | | | | | | | | | | | | | | | | | | | | | | |
| | Endocrine dis. | yes | | | | | | | | | | | | | | | | + | | | | | | |
| Pregnancy factors | Vomiting | Severe | | | | | + | | | | | | | | | | | | | | | | | |
| | | mod. | | | | | | | | | | | | | | | | | | | | | | |
| | | none | | | | | | | | | | | | | | | | | | | | | | |
| | Toxemia | yes | | | | | | | | | | | | | | | | | | | | | | |
| | Diet | good | | | | | | | | | | | | | | | | | | | | | | |
| | | bad | | | | | + | | | | | | | | | | | | | | | | + | |
| | | fair | | | | | | | | | | | | | | | | | | | | | | |
| Environment | Poverty | yes | | | | | | | | | | | | | | | | | | | | | | |
| | Poor hygiene | yes | | | | | | | | | | | | | | | | | | | | | | |
| | Overwork | yes | | | | | | | | | | | | | | | | | | | | + | | |
| | Casual mother | yes | | + | | | | | | | | | + | | | | | | + | + | | + | | |
| Child's health | Allergy | yes | | | | | | | | | | | | | | | | | | | | | | |
| | | slight | | | | | | | | | | | | | | | | | | | | | | |
| | | none | | | | | | | | | | | | | | | | | | | | | | |
| | Illnesses | few | | | | | | | | | | | | | | | | | | | | | | |
| | | mod. | | | | | | | | | | | | | | | | | | | | | | |
| | | many | | | | | | | + | | | | | | + | | | | | | + | | + | |
| | Nutrition | good | | | | | | | | | | | | | | | | | | | | | | |
| | | average | | | | | | | | | | | | | | | | | | | | | | |
| | | poor | | | | | | | | | | | | | | | | | | | | | | |
| Diet | Breast | no | | | | | | | | | | | | | | | | | | | | | | |
| | | newborn | | | | | | | | | | | | | | | | | | | | | | |
| | | yes | | | | | | | | | | | | | | | | | | | | | | |
| | Protein | good | | | | | | | | | | | | | | | | | | | | | | |
| | | poor | | | | | | | | | | | | | | | | | | | | + | | |
| | | fair | | | | | | | | | | | | | | | | | | | | | | |
| | Cereals | good | | | | | | | | | | | | | | | | | | | | | | |
| | | poor | | | | | | | | | | | | | | + | | | | | | + | | + |
| | | fair | | | | | | | | | | | | | | | | | | | | | | |
| | Fruits and vegetables | good | | | | | | | | | | | | | | | | | | | | | | |
| | | poor | | | | | | | | | | | | | | | | | | | | | | |
| | | fair | | | | | | | | | | | | | | | | | | | | | | |
| | Sweets | no | | | | | | | | | | | | | | | | | | | | | | |
| | | mod. | | | | | | | | | | | | | | | | | | | | | | |
| | | many | | | | | | | | | | | | | | | | | | | | | | |
| Vitamins | A and D | good | | | | | | | | | | | | | | | | | | | | | | |
| | | poor | | | | | + | | + | | + | | | | | | | | | | | | | |
| | | fair | | | | | | | | | | | | | | | | | | | | | | |
| | B and C | poor | | | | | | | | | | | | | | + | | | | | | + | | + |
| Adverse factors per child in all groups | | | | 1 | 0 | 0 | 1 | 4 | 2 | 1 | 2 | 0 | 2 | 1 | 2 | 4 | 1 | 2 | 2 | 3 | 1 | 5 | 2 | 3 |
| Adverse factors per child in Ratio+ groups | | | | 1 | 0 | 0 | 1 | 4 | 1 | 0 | 2 | 0 | 2 | 1 | 1 | 1 | 0 | 2 | 1 | 1 | 1 | 1 | 1 | 2 |
| Attendance at clinic | | infancy | | | | | | | | | | | | | | | | | | | | | | |
| | | later | | | | | | | | | | | | | | | | | | | | | | |
| Average number of visits last four years | | | | | | | | | | | | | | | | | | | | | | | | |

TABLE 1

| 19 20 21 | 22 23 24 25 26 27 | TOTAL | % | GROUP C 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 | TOTAL | % |
|---|---|---|---|---|---|---|
| | | 17.0 | 63.0 | | 1.0 | 5.6 |
| + | + | 9.0 | 33.3 | + + + + + + + + | 12.0 | 66.6 |
| | | 1.0 | 3.7 | | 5.0 | 27.7 |
| | | 10.0 | 37.0 | | 6.0 | 33.3 |
| + + | + + + + | 12.0 | 44.4 | + + + + | 5.0 | 27.7 |
| | | 5.0 | 18.5 | | 7.0 | 38.8 |
| | | 26.0 | 96.3 | | 14.0 | 77.8 |
| | | 1.0 | 3.7 | + + + + | 4.0 | 22.2 |
| | | 0.0 | | | 0.0 | |
| | | 0.0 | | + + | 2.0 | 11.1 |
| | | 1.0 | 3.7 | | 0.0 | |
| | + | 2.0 | 7.4 | + + + | 4.0 | 22.2 |
| | | 1.0 | 3.7 | | 2.0 | 11.1 |
| | | 24.0 | 89.0 | | 12.0 | 66.7 |
| | + | 1.0 | 3.7 | | 0.0 | |
| | | 13.0 | 48.0 | | 6.0 | 33.3 |
| + | + | 3.0 | 11.0 | + + + + | 5.0 | 27.7 |
| | | 11.0 | 40.7 | | 7.0 | 38.8 |
| | | 0.0 | | + + + | 3.0 | 16.6 |
| | | 0.0 | | + | 1.0 | 5.6 |
| + | | 1.0 | 3.7 | + + + | 2.0 | 11.1 |
| + | + | 6.0 | 22.2 | + + + + + + + + + | 10.0 | 55.6 |
| | | 0.0 | | | 1.0 | 5.6 |
| | | 4.0 | 15.0 | | 1.0 | 5.6 |
| | | 23.0 | 85.0 | | 16.0 | 88.8 |
| | | 13.0 | 48.0 | | 9.0 | 50.0 |
| | | 10.0 | 37.0 | | 6.0 | 33.3 |
| + | | 42.0 | 15.0 | + + | 2.0 | 11.1 |
| | | 14.0 | 51.8 | | 13.0 | 72.2 |
| | | 7.0 | 29.6 | | 5.0 | 27.7 |
| | | 6.0 | 22.2 | | 0.0 | |
| | | 11.0 | 40.7 | | 3.0 | 16.6 |
| | | 5.0 | 18.5 | | 1.0 | 5.6 |
| | | 11.0 | 40.7 | | 14.0 | 77.8 |
| | | 19.0 | 70.3 | | 12.0 | 66.7 |
| + | | 1.0 | 3.7 | + + | 2.0 | 11.1 |
| | | 7.0 | 29.6 | | 4.0 | 22.2 |
| | | 12.0 | 44.4 | | 10.0 | 55.6 |
| + | + + | 4.0 | 15.0 | + + | 2.0 | 11.1 |
| | | 11.0 | 40.7 | | 6.0 | 33.3 |
| | | 26.0 | 96.3 | | 14.0 | 77.8 |
| | | 0.0 | | | 0.0 | |
| | | 1.0 | 3.7 | | 4.0 | 22.2 |
| | | 11.0 | 40.7 | | 3.0 | 16.6 |
| | | 16.0 | 59.3 | | 10.0 | 55.6 |
| | | 0.0 | | + + + + + | 5.0 | 27.7 |
| | | 20.0 | 74.0 | | 7.0 | 38.8 |
| | | 3.0 | 11.0 | + + + + | 4.0 | 22.2 |
| | | 4.0 | 15.0 | | 7.0 | 38.8 |
| + | + + | 4.0 | 15.0 | + + | 2.0 | 11.1 |
| 5 2 3 | 3 3 1 3 2 1 | 52.0 | | 7 2 2 8 1 4 4 1 5 4 3 4 2 3 6 2 4 3 | 66.0 | |
| 1 1 2 | 0 0 0 2 2 1 | 27.0 | | 6 1 2 8 1 2 3 1 4 3 3 2 1 3 5 2 3 2 | 52.0 | |
| | | 21.0 | 77.7 | | 13.0 | 72.3 |
| | | 6.0 | 22.3 | | 5.0 | 27.7 |
| | | 7.9 | | | 6.1 | |

TABLE II

| | | | GROUP A % | GROUP C % | RATIO A TO C |
|---|---|---|---|---|---|
| Familial factors: | Mother's teeth: | good | 63.0 | 5.6 | |
| | | poor | 33.3 | 66.7 | 1 to 2 |
| | | fair | 3.7 | 27.7 | |
| | Father's teeth: | good | 37.0 | 33.3 | |
| | | poor | 44.4 | 27.7 | no |
| | | fair | 18.5 | 38.8 | |
| Maternal, all adverse factors | | | 7.4 | 33.3 | 1 to 4.5 |
| Pregnancy, all adverse factors | | | 22.2 | 50.0 | 1 to 2 |
| Environment, all adverse factors | | | 3.7 | 33.3 | 1 to 9 |
| The casual mother | | | 22.2 | 55.6 | 1 to 2.5 |
| Child's health, all adverse factors | | | 15.0 | 11.1 | no |
| Nutrition: | above average | | 51.8 | 72.2 | |
| | average | | 29.6 | 27.7 | no |
| | below average | | 22.2 | 0.0 | |
| Diet: Breast feeding | | no | 40.7 | 16.6 | |
| | | newborn | 18.5 | 5.6 | no |
| | | yes | 40.7 | 77.8 | |
| Protein, cereal, fruit, vegetable (taken poorly) | | | 18.5 | 15.0 | no |
| Sweets | | little | 40.7 | 16.6 | |
| | | moderate | 59.3 | 55.6 | |
| | | much | 0.0 | 27.7 | high |
| Vitamins A and D | | good | 74.0 | 38.8 | |
| | | poor | 11.0 | 22.2 | 1 to 1.7 |
| | | fair | 15.0 | 38.8 | |
| Attendance at center | | infancy | 77.7 | 72.3 | no |
| | | later | 22.3 | 27.7 | |
| Average number visits during dental study | | | 7.9 | 6.1 | no |
| Average adverse factors per child | | Group A 1.9 | Group B 2.4 | Group C 3.66 | Ratio A to C 1 to 2 |
| Average adverse factors per child in divisions showing a positive correlation | | 1.0 | | 2.90 | 1 to 3 |

sugars, particularly in the form of candy, is of distinct significance and a low vitamin A and D intake may also play a role.

Two siblings in the study were of particular interest. During the pregnancy of one the mother was in Russia and on what she describes as a starvation diet, markedly limited in proteins and vitamins. The family came to the United States during this child's infancy and from then on the diet was well supervised and adequate. The second child was born in this country, the mother had a normal pregnancy, and the child's infancy paralleled that of the firstborn. The first child is in Group C with rampant caries and the second in Group A. A single incident of this type is suggestive but not conclusive.

It should not be forgotten that the adverse factors which have no obvious effect on the first teeth may be playing a role in the susceptibility of the second teeth to decay.

When the adverse factors are added vertically in Table I, the number of these per child is obtained. In Group A these numbers vary from

0 to 5; in Group C 1 to 8. If only the adverse factors of the divisions showing a positive correlation are added, the figure for Group A is 0 to 4 and for Group C it is 1 to 8. The distribution of the children in the two groups according to adverse factors per child is represented in Fig. 1. The interesting individuals to note are the exceptions in each group; that is, the children with four adverse factors who have no caries and the ones with only one adverse factor who still develop rampant caries. The pediatrician will recognize this type of child as a recurrent problem in his practice. Patient No. 5 in Group A with four adverse factors checked against her has perfect teeth. She has been followed very closely and is now 10 years of age. Her second teeth are as good as her first, and her mother states that her "shed" teeth were without caries. In Group C there are four children with

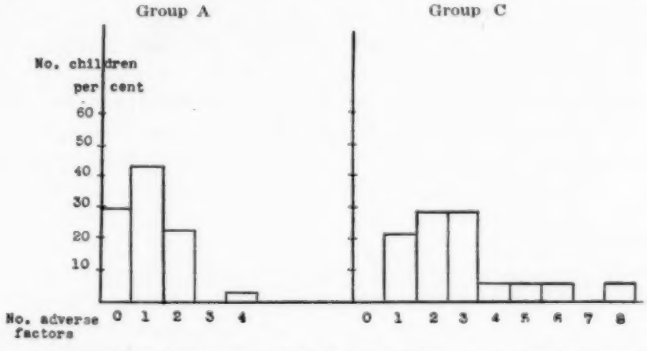


Fig. 1.—Distribution of children according to the number of adverse factors per child.

only one adverse factor and yet they have marked caries. Only one of these four gives a history of excessive sweets. Three of these children have attended the center very faithfully and the mothers have been very conscientious. This is the type of child who is referred to the pediatrician by the dentist with some such recommendation as "Please check this child's diet," or the dentist, without consulting the pediatrician, places the child on a diet with cod-liver oil, and calcium. Others interested in research will, by probing deep and long, obtain a history which might be interpreted as "high sugar intake," "poor vitamin D intake." On the basis of an unbiased observational study of this type, such conclusions are unsound. Surely the observations and records made from month to month on a child are more reliable than probings made in retrospect after caries have been discovered. Mothers' memories are notoriously unreliable. There are several children in the noncarious Group A with much worse histories than the children in Group C. Some other factor must be considered; the most likely explanation of these exceptions is teeth structurally bad, probably on an hereditary basis.

## COMMENTS

An observational study of this type does not lend itself readily to scientific conclusions, but it offers suggestions and warnings. The study suggests that the teeth, like other organs of the body, vary intrinsically within a wide range and the end results, as expressed in caries, may be dependent on many factors. With many adverse factors in operation, the best teeth may decay; conversely with the best of care, the structurally inadequate teeth may succumb to caries. The study suggests further that the first teeth are more influenced by prenatal factors than postnatal ones, and of the postnatal factors excessive sweets and lack of vitamin A and D probably are the most important recorded in this study.

This study warns emphatically against the use of loosely constructed human control experiments. Where multiple factors are involved, most of which are beyond control, the result from controlling one factor is masked by the influences of the uncontrolled factors. For example, if these 78 children had been divided into two groups at the beginning of the study and one-half given cod-liver oil and the other one-half none, the results would almost certainly have been negative or the variations would have been so slight that conclusions drawn would be subject to grave doubt. The natural variations offset the experimental constants. In an individual case, however, the cod-liver oil may be the important factor. It is too bad that the laboratory-controlled experiment has been accepted as practically the only prototype for a study of clinical problems. The human animal does not lend himself to this type of study. Only the few experiments on identical twins or the use of a specific drug in a highly fatal disease, such as the use of sulfanilamide in newborn erysipelas, can be considered as in any way approaching a controlled experiment. In most types of human studies, however, the variations in race, size, age, heredity, environment, habits, and will power summed up will mask the expected results in individual cases. Negative results obtained in such a study should not and cannot logically be used as positive proof against the value of a given factor in an individual case. The clinician can well afford to observe carefully, weigh honestly, and draw some of his own conclusions on individuals under his care and also view more critically statistical studies and experimental results that come out of laboratories based too often on animal experiments and interpreted for humans on such a basis.

James Hilton has put this concept aptly in a recent article when he says, "Though our insurance company knows to a month how long ten thousand of us will live, it knows no more about what will happen to you and me tomorrow than we ourselves do."

## SUMMARY

A group of children attending a health center from infancy has been studied and compared for the presence of caries in the first dentition.

Pertinent data were recorded on family and maternal history, pregnancy, and child's eating habit. Just before the first teeth were "shed," the children were grouped into three groups, depending on the number and extent of caries, and then Group A with near perfect teeth was compared with Group C, suffering with rampant caries.

The factors in Groups A and C showing a positive high correlation were:

1. The condition of the mothers' teeth.
2. Adverse factors in the maternal history, such as elderly mothers, ill health, etc.
3. Adverse factors during pregnancy, such as poor diet, vomiting, toxemia.
4. Adverse environmental factors, such as poverty, poor hygiene, casual care.
5. There was a high correlation between sugar intake and caries and a less marked one between the low intake of vitamins A and D and caries.

There was no correlation between childhood illnesses, nutrition as gauged by height, width, weight charts, breast feeding, or diet per se in the A and C groups.

The attendance at the center of the two groups was comparable.

# VITAMIN $B_6$ (PYRIDOXINE HYDROCHLORIDE) IN THE TREATMENT OF PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY AMONG CHILDREN

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IN MARCH, 1940, Antopol and Schotland[1] reported a series of cases in which pseudohypertrophic muscular dystrophy was treated successfully by means of subcutaneous and intravenous injection of vitamin $B_6$. They treated six patients and stated that there was considerable improvement in their condition in as short a time as three or four weeks. Indeed, in two cases they noted some improvement one-half hour to three hours after the administration of 50 mg. of the vitamin. Vitamin $B_6$ was given in doses of 10 to 500 mg. every four to seven days. They did not find any untoward effects whatever. They stated that their patients were not cured but were still under treatment.

Because of the promising therapeutic effect we treated ten patients who had undoubted pseudohypertrophic muscular dystrophy for periods of four to eight months. The pyridoxine was generously supplied by the Abbott Laboratories of North Chicago, Ill. It was given intramuscularly at intervals of two to seven days in doses of 100 mg. (at first a few patients received 200 mg. at each injection) and the total amounts given were from 1.8 to 3.7 Gm. of pyridoxine hydrochloride.

Five of the patients treated were unable to stand or walk and were all aged 10 to 12 years. Two were 7 and 9 years old, respectively, and walked with marked lordosis and typical waddling gait. The remaining three were 3 years, 9 months, 4 years, 7 months, and 5 years old, respectively, and were typical, but were able to walk without much assistance. All our patients were boys.

Muscular dystrophy of the type discussed here is a very slowly progressive disease. It is difficult to estimate changes in the strength of various muscles or in the patient's general muscular strength. To attempt to overcome this difficulty, in part at least, we devised a simple apparatus of rope, weights, pulley, and arm and foot rests by means of which we could test the strength of the pectoral muscles or of the gluteal muscles (Figs. 1 and 2). With the patient sitting on the examining table with the right or left arm in rest at right angles to the body, it was possible to measure the height to which he could raise various weights. The same apparatus was fitted with movable and fixed canvas boots and with the patient in a prone position on a table the

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"pulling" or "weight lifting" strength of the gluteal muscles could be measured roughly when the patient raised his foot upward and backward.

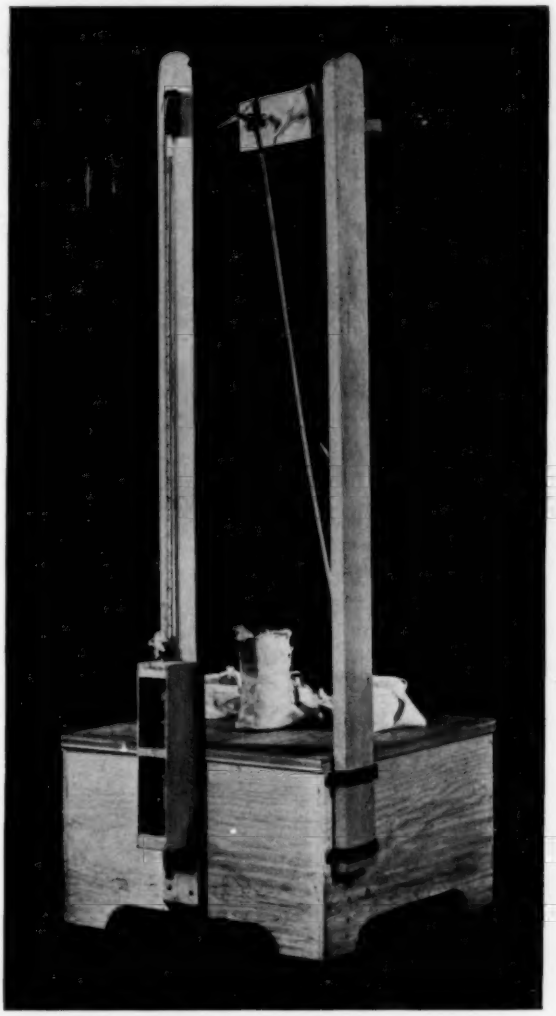

Fig. 1.—Apparatus for testing strength of pectoral muscles.

## CASE REPORTS

CASE 1.—This boy was first examined in 1938 at the age of 7 years. He had begun to walk at 1 year of age but always had had a clumsy, waddling gait and difficulty in climbing stairs. Since the age of 3 or 4 years his calf muscles were noticeably enlarged. He was fairly well nourished and of approximately the correct weight for his height. There was marked weakness of the muscles of the shoulder

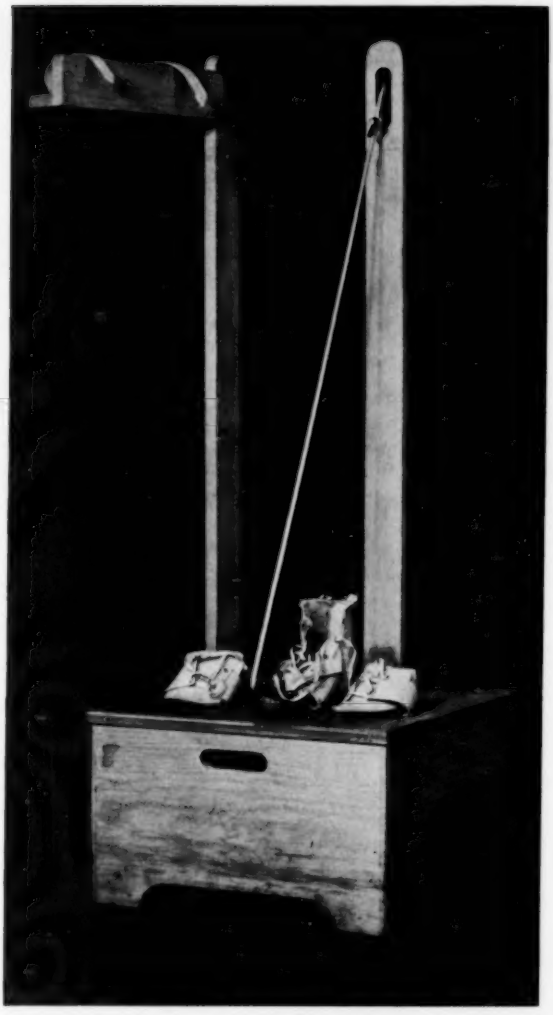

Fig. 2.—Same apparatus as in Fig. 1 used to test strength of the gluteal muscles.

girdle as well as generalized weakness. The gastrocnemii were large and firm and the patient "climbed up his legs" when rising from the prone position. His gait was waddling and there was marked lumbar lordosis. In August, 1940, his lordosis had increased, and the abnormal gait was still more accentuated. He was given weekly injections of vitamin $B_e$ for thirty-two weeks, a total of 3.7 Gm. During this time not only was there no increase in strength, but a definite decrease occurred so that he had to be lifted up when he fell. At the same time measurements of the pulling strength of the pectoralis muscles showed little change except perhaps a slight decrease in strength.

CASE 2.—This boy was first examined at the clinic in 1935 at the age of 6 years. It was said that he appeared to be a normal baby until he began to walk at the age of 1 year. At that time it was noted that he was unusually clumsy and the calves of his legs were larger than might be expected. The enlargement of the legs had persisted and he had had progressive difficulty in walking and in climbing stairs; otherwise the boy had seemed normal. Examination showed generalized muscular weakness. The calf muscles of both legs were very much enlarged. The knee jerks were obtained with difficulty. In getting up from the prone position the boy "climbed up his legs." On August 12, 1940, at the age of 11 years he was re-examined. In the interval he had become progressively weaker and had been unable to walk for at least two years. He was, however, able to go to school in a wheel-chair and could use his hands for lifting books, for taking food, and for very light effort. He was unable to raise a full glass of water to his mouth with one hand. Beginning in August, 1940, he was given 100 mg. of vitamin $B_6$ intramuscularly at approximately weekly intervals until April 10, 1941, when he had had a total of 3.3 Gm. During this eight months there had been practically no change in his condition. His mother stated at one time that he was able to operate the push buttons on a new radio which he had been unable to do before. Measurement of the strength of the pectoralis muscles, however, showed that there was little if any change but that they were perhaps a little weaker after the eight months of treatment.

CASE 3.—This boy was first examined at the clinic in July, 1940, at the age of 5 years. When he was very young, his mother had noticed that the muscles of the legs were large and firm, but he did not have any trouble in learning to walk. It was noted, however, that there was some weakness of the leg muscles and that he walked with a peculiar waddling gait although this latter was not very marked. Examination showed the boy to be rather thin. There was considerable weakness of the muscles of the shoulder girdle. The arms were rather thin; the muscles hard, particularly the triceps. The calf muscles were large and hard. The boy walked with a definite waddling gait and got up from the floor slowly "climbing up his legs." He was a member of a family of six children, three of them (all boys) having pseudohypertrophic muscular dystrophy. On July 29 he was given 100 mg. of vitamin $B_6$ intramuscularly and this was repeated at weekly intervals for fifteen weeks. In all, this boy had 2.6 Gm. of vitamin $B_6$ intramuscularly. During this time there was no essential change in his condition. Comparative measurements of the strength of the pectoralis muscles and of the gluteal muscles showed perhaps a slight increase in strength. This boy, however, was quite young and very apprehensive during the earlier examination. The apparent increase in the muscular strength may have been due to the fact that he was more familiar with the apparatus. When examined nine months after the treatment had been instituted the patient seemed definitely weaker. The increase in weakness was confirmed by his mother and by tests of the strength of the pectoralis and gluteal muscles.

CASE 4.—This boy was first examined at the clinic on July 29, 1940, at the age of 3 years, 9 months. This child had two older brothers who suffered from pseudo-hypertrophic muscular dystrophy. His mother noted that when he was a few months old his leg muscles were unusually large but he learned to walk at approximately 13 months of age. Examination showed him to be quite well nourished, weighing 35½ pounds (16.1 kg.). The muscles of the shoulder girdle were noticeably weak. The calf muscles were larger and firmer than usual and felt irregularly hard. The child walked easily enough but with a waddling gait. In getting up from the floor he attempted to "climb up his legs." Beginning July 29, 1940, he was given 100 mg. of vitamin $B_6$ intramuscularly at weekly intervals for a period of sixteen

weeks. During this period he was given a total of 2.7 Gm. There was no essential change in his condition, and six months after treatment had been stopped, his mother stated that he was approximately the same but perhaps a little weaker. During the period of treatment an attempt was made to measure the strength of the pectoral muscle and gluteal muscle by a weight lifting device. The boy, however, was so small that co-operation was not very satisfactory. There appeared to be slight improvement in the strength but this was felt to be due to his increased familiarity with the apparatus. Nine months after treatment was begun and six months after it had been stopped muscle tests showed no essential loss or gain.

CASE 5.—This boy was first examined at the clinic on July 7, 1936, at the age of 6 years. The mother noted that when this boy was 4 years old there was definite weakness of the legs. This had increased definitely during the two years before admission and he had been falling down rather frequently. When he fell down he assumed the erect posture again by "climbing up his own legs." Examination showed him to weigh 39 pounds (17.7 kg.), approximately the correct weight for his height and age. He had the peculiar waddling gait typical of patients who have muscular dystrophy. It was noted that the calf muscles of both legs were unusually large for a boy of his age. He was again examined on July 29, 1940. During the interval from July, 1936, to July, 1940, he had become very much weaker, had gained a considerable amount of weight, was unable to walk or to stand, and raised his hands from his knees only by tipping his shoulders backward. There was marked contracture of the calf muscle. When sitting in his chair he was able to move his legs only through an arc of 20 to 25 degrees. Beginning July 29 this boy was given 100 to 300 mg. of vitamin $B_6$ intramuscularly at weekly intervals. This was continued over a period of sixteen weeks. During this time he had a total of 3.2 Gm. of vitamin $B_6$. During this period of sixteen weeks there was no change in his condition that we could note, and in the five months since treatment was stopped no particular change has occurred.

CASE 6.—This boy was first examined at the clinic on July 22, 1940, at the age of 4½ years. In infancy he had seemed normal. He did not stand or walk, however, until he was 20 months old. At 2 years of age he was able to pull himself up onto his feet. At 3 years he had improved somewhat but reached a standing position by "climbing up his own legs." At this time a diagnosis of pseudohypertrophic muscular dystrophy was made. Examination showed him to be slightly over the average weight for his height. There did not seem to be much generalized muscular weakness. The calf muscles of both legs, however, were quite large and firm. In getting up from the floor he climbed to his hands and knees, then his feet, and then with his hands on his knees pushed himself erect. His gait was of the waddling type with a rather wide base. The muscles of the shoulder girdle did not seem to be unusually weak. The diagnosis of pseudohypertrophic muscular dystrophy was confirmed and treatment with vitamin $B_6$ was started. One hundred or 200 mg. was given every second or third day until 1.1 Gm. had been given. After leaving Rochester he was given vitamin $B_6$ at weekly intervals until 2.4 Gm. more of the vitamin had been given. This patient was not examined again at the clinic. His parents, however, reported from time to time and stated that there was no definite change in his condition. Eight months after treatment had been begun his mother stated that his general health was good but that he was not climbing stairs any better and that his strength apparently had not increased.

CASE 7.—The patient was first examined at the clinic on March 15, 1937, at the age of 9 years. His parents stated that he had been a normal chubby baby at birth and started to walk at the age of 17 to 18 months in a normal enough manner. They did note, however, that he was a little slow and stumbled more readily than the

other children. At the age of 6 years it was noted that the boy had trouble getting up from the sitting or lying position and that he did this by pushing himself up rather than by reaching out and pulling himself. This particular difficulty had become progressively more noticeable. Examination showed the boy to be approximately 20 pounds (9.1 kg.) more than the estimated weight for his height. He was unable to get up to a standing position without considerable assistance. He was able to walk only after being put in the proper position. There was marked lumbar lordosis. There was considerable enlargement of the calf muscles of both legs as well as atrophy and weakness of the muscles of the shoulder girdle. The boy was examined again at the clinic on August 30, 1940, at the age of 12 years. At this time his parents stated that he had been unable to walk for approximately three years. His general weakness had become much more pronounced. He was still considerably overweight, but otherwise appeared well. He was scarcely able to sit alone. There was contraction of the calf muscles of both legs. He was unable to raise his arms at all but was able to hold up his head quite readily. Vitamin $B_6$, 100 mg., was given on August 30 and again 100 mg. was given on August 31. This patient was unable to remain for further treatment but he was given 100 mg. weekly at home for a period of twelve weeks, making a total of 1.4 Gm. of vitamin $B_6$. In a recent report his mother stated that the injections seemed to make no difference whatever in his condition, that there was, if anything, an increase in the weakness. For example, if his head fell backward or to the side he could not get it back into the erect position without assistance.

CASE 8.—The patient was first examined at the clinic in August, 1934, at the age of 6 years. The presenting symptom was difficulty in climbing stairs. He was slow in learning to walk, not walking alone until he was 22 months old. His parents stated that he had to use his hands to help himself when going upstairs and that he did not run with any facility. The examination showed him to be of approximately the correct weight for his height; namely, 42 pounds (19.1 kg.). It was noted that he had some lumbar lordosis but his gait was not particularly unusual. The muscles of the shoulder girdle showed little if any weakness. The calves of both legs were a little larger than might be expected. It was felt that this patient had definite pseudohypertrophic muscular dystrophy but that it was very mild and very slowly progressive. The patient was re-examined in July, 1937. He had been taking 1 teaspoonful (4 c.c.) of glycine and 1 teaspoonful of glutamine three times a day. His father felt that he had more generalized weakness and stated that he could no longer walk upstairs but walked well on the level. There was definite weakness of the muscles of the shoulder girdle. The lordosis was marked. It was felt that there was considerable progression since the examination three years previously. The patient was again examined in July, 1940. The weakness had been slowly progressive and for two years he had been unable to walk and was confined entirely to a chair. He had gained considerable weight during the previous two years. He continued to do well in school as he always had done. He was unable to get up or to sit alone and there were definite contractures of the gastrocnemii. On August 12, 1940, he was given 100 mg. of vitamin $B_6$ intramuscularly. During the next week he was given five doses of 200 mg. each. During the next twenty weeks he received approximately 2 Gm. of vitamin $B_6$ intramuscularly. A recent report from his father stated that his strength did not improve during or after treatment.

CASE 9.—This patient was examined at the clinic in April, 1939, at the age of 9 years. The presenting symptom was muscular weakness which had been noticeable since the age of 4½ years. At this time he seemed to fall frequently because his knees buckled under him. Since that time it had been noted that he had been getting weaker in both arms and legs. One year before examination he could easily climb

up himself to an erect position but within the few months before coming to the clinic he had been unable to do this. His parents stated that three years before the muscles of the calves of both legs were large and hard but that within the previous year the muscles had become much smaller. They also stated that there had been progressive loss of strength of the muscles of the shoulder girdle during the previous two years. Examination showed the boy to be slightly less than the average weight for his height. He was unable to walk well. He walked with a wide base and definite lumbar lordosis. He was unable to rise from the floor without considerable assistance. There was definite atrophy of the muscles of the shoulder girdle. The legs seemed small except that the gastrocnemius muscles were firm. The patient had a rather typical waddling gait. It was felt that he had extensive evidence of pseudohypertrophic muscular dystrophy. He was examined again in July, 1940. During the interval he had gained in weight and had become somewhat taller. His strength, however, had not kept pace with his gain in weight and he was unable to stand or to walk. His arms were apparently no weaker than they had been the year before. He had been taking concentrated vitamin E for three months without any increase in strength. Examination showed him to be 6 pounds (2.7 kg.) more than the estimated weight for his height. On July 26 administration of vitamin $B_6$ was begun, 100 mg. intramuscularly. This was repeated on the following day. Two days later the patient was given 200 mg. He then left the clinic and his treatment was carried on at home. He was given 200 mg. a week and then 100 mg. a week until he had had a minimal total of 2.6 Gm. of vitamin $B_6$. His physician at home reported as follows: "No definite evidence of increased muscle tone or strength was present. Vitamin $B_6$ in this case was of no value."

CASE 10.—This patient was first examined at the clinic in August, 1939, at the age of 6 years. The presenting symptoms were clumsiness in walking and large hard muscles. The parents stated that since he had begun to walk at the age of 18 months, he had been clumsy, stumbling and tripping frequently. When climbing stairs he grasped the left knee when placing that foot down on the next step as though uncertain where it was going. When rising from a prone position he grasped both knees and "climbed up himself." The mother had noted also that the muscles of the calves of both legs and forearms were large and hard; yet there was considerable weakness. Examination showed the boy to be of approximately the correct weight for his height. The deltoid muscles on both sides and the muscles of the forearms and the calves of the legs were hard and large. There was generalized muscular weakness, but otherwise the results of his examination were not unusual. The boy returned for further observation in August, 1940. At that time he seemed quite active and walked without much difficulty but with a rather waddling gait. He was able to ride a tricycle but any little elevation bothered him and he had to be helped frequently. There was considerable weakness of the muscles of the shoulder girdle and of the pectoralis muscle. He was unable to lift his head from the pillow when lying on his back. The muscles of the calves of both legs were very large and firm. Treatment was immediately begun with intramuscular administration of 100 mg. of vitamin $B_6$. This was repeated at weekly intervals until at least 1.2 Gm. of vitamin $B_6$ had been given. The boy's mother reported that after treatment his strength was not increased, and the treatment did not help him.

## COMMENT

It was evident in observing these children over a period of several months that there was little change in their condition. Six of the patients were treated and examined in the clinic at weekly intervals. One certainly could not see any improvement in strength, and in three of them there was definite decrease in their ability to walk or execute

other movements. In the two patients who cooperated most satisfactorily in carrying out the muscle tests and who, incidentally, had the most consistent treatment over the longest period, there was a definite decrease in the strength of the muscles tested. One child was too young for us to obtain good cooperation. In the case of one child who seemed to show slight improvement in the strength of the gluteal muscles, his mother volunteered the information that he seemed to be having "more trouble walking." The fifth patient having muscle tests seemed to show slight improvement in the strength of the arms, but he was observed for a short period only. His mother later reported that his strength was not increased. We were unable to do muscle tests on the sixth patient under our own observation as he was too weak to operate the apparatus. Four of the patients have been treated and observed by their family physician. None of the four have shown any improvement in spite of fairly persistent treatment and the latter has been stopped.

Although improvement has been noted by others[1, 2] after single injections or after one month of treatment with vitamin $B_6$, we have been unable to show any improvement after as long as eight months of similar treatment. In fact the two patients that received the treatment most consistently and over the longest period showed definite decrease in strength. This is in agreement with the findings of Ferrebee and coworkers[3] and Doyle and Merritt[4] who found that both vitamin $B_6$ and vitamin E had no effect on various types of neuromuscular diseases, including pseudohypertrophic muscular dystrophy. However, in confirmation of the reports of others, we did not see any deleterious effect either local or general after the injection of pyridoxine hydrochloride. The appetite and general condition of the patients were reported as improved by all the parents.

## CONCLUSIONS

The intramuscular injection of vitamin $B_6$ in amounts from 100 to 200 mg. weekly for periods of from two months to eight months did not produce any measurable improvement in the strength of the pectoralis and gluteal muscles or any increase in general muscular strength that could be noted.

Vitamin $B_6$ in these amounts did not have any deleterious effect, either general or local.

Since this paper was written, an article by McBride and Baker has appeared in THE JOURNAL OF PEDIATRICS in June, 1941. In this article they stated that vitamin $B_6$ administered orally and intravenously was ineffective for treating pseudohypertrophic muscular dystrophy.

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# ACUTE YELLOW ATROPHY OF THE LIVER

## Report of a Case in a Twelve-Year-Old Girl With Autopsy Findings

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ACUTE yellow atrophy of the liver is a comparatively infrequent disease in all age groups. About 50 per cent of the cases have been reported in patients between 20 and 30 years of age and somewhat less than 10 per cent in patients below 10 years of age. Philips[1] found records of only 38 cases in the literature from 1860 to 1912 and added two of his own. Herxheimer[2] collected 78 instances of the disease up to 1922 but failed to include eleven cases mentioned by Philips. We have been able to gather information on 126 cases, including those mentioned by other reviewers[1, 2, 3, 4, 5] and report an additional case with autopsy findings. Eleven cases were reported in the newborn period, one in association with scleroderma.[6] The ages of the 127 patients are given in Table I.

Table I

| AGE | NUMBER OF CASES |
|---|---|
| Newborn | 10 |
| Under 1 yr. | 13 |
| From 1 to 10 yr. | 88 |
| 10 to 15 yr. | 11 |
| Age unknown | 5 |

Of 95 cases in which sex was mentioned, 53 occurred in males and 42 in females.

### CASE REPORT

A female child of 12 years of age was admitted on Dec. 1, 1939, with a history of nausea and vomiting for two weeks, pruritus for one week, and jaundice of the face and sclerae for three days prior to admission. There were no cases of jaundice or influenza in the vicinity of her home, and there was nothing in the personal or family history of etiologic significance.

Physical examination on admission revealed a well-developed and well-nourished girl with essentially negative findings except for a moderate jaundice. The skin and sclerae were moderately icteric, the stools were clay colored, and the urine bile-tinged. There were no evidences of liver enlargement on either palpation or percussion.

The laboratory findings at this time included positive urobilinogen in dilution of 1 to 50 but negative in 1 to 75, an icterus index of 48.6, an immediately strong positive direct van den Bergh reaction, and a blood cholesterol of 210 mg. per 100 c.c. with 60 per cent free cholesterol and 40 per cent of cholesterol esters.

From the Service of Dr. M. B. Gordon, Department of Pediatrics, Israel Zion Hospital.

On the basis of the history, the general appearance of the patient, and the laboratory findings, a diagnosis was made at this time of so-called catarrhal jaundice or acute hepatitis.

The child was placed on a high carbohydrate diet, fruit juices, and skimmed milk. There was no change in the general well-being for the first week except for an increase in the intensity of the jaundice and a rise in the icterus index to 75.8.

The liver did not show any enlargement until the thirteenth day after admission when it was easily palpable for one finger's breadth below the free costal margin. The liver edge could be felt for two days and then it receded.

Vomiting set in on the ninth day and became progressively worse until the demise. The jaundice continued to increase in intensity with a concomitant rise in the icterus index. The general condition changed, the child lost her genial disposition and became apprehensive, and the skin lost its resiliency and became dehydrated because of the increasing toxicity and continued vomiting in spite of parenteral administration of glucose solution.

On December fifteenth the patient suddenly became irrational with alternating periods of hyperactivity and sleep. On the next day coma set in. A Babinski reflex was elicited on the right side. The icterus index had risen to 160. A spinal puncture at this time revealed a fluid which was slightly xanthochromic but with negative chemical, cytologic, and bacteriologic, findings. Leucine and tyrosine crystals were absent in the urine.

The temperature remained around 99° F. throughout the entire illness except for a preterminal rise to 102° and then to 106° on the day of death, which occurred sixteen days after admission to the hospital.

The treatment consisted of the administration of large amounts of carbohydrates by mouth and by hypodermoclysis.

*Laboratory Findings.*—The chemical findings in the blood were within normal levels except those for cholesterol. The latter rose from an initial value of 210 mg. per 100 c.c. with 60 per cent free cholesterol on the day of admission to 310 mg. and 71 per cent free cholesterol twelve days later. The icterus index rose steadily from 48 to 150; a strongly positive immediate direct van den Bergh reaction was present throughout the entire course. There was increased fragility of the red blood cells; hemolysis commenced at 0.475 and was complete at 0.28. Both the coagulation and bleeding times were prolonged. Urinalyses gave essentially normal findings on several occasions except for the presence of urobilinogen in dilution of 1 to 50 and, later, of 1 to 100.

*Post-Mortem Findings* (Dr. Jacob Ravid).—Autopsy revealed a degenerative hepatitis with acute yellow atrophy of the liver, arteriosclerosis of the splenic vessels, subpleural and interlobar hemorrhages of the lower lobes of both lungs, and subepicardial and endocardial hemorrhages of the left ventricle.

On microscopic examination, the parenchyma of the liver was found to be almost completely destroyed. The destruction was most marked in the central portion of the lobules and only a very narrow, irregular rim of periportal tissue with regeneration remained. The entire structure was edematous and consisted mainly of almost completely necrotic material. Here and there were noted a few discrete islands which were apparently remnants of the portal canal. These contained numerous round cells and occasional fibroblasts in addition to clusters of regenerating liver cords. The few remnants of periportal spaces contained collections of round cells and a number of irregular, somewhat hyperplastic proliferating bile ducts which extended from the periphery into the central portion of the lobules. Isolated cords with distinct regeneration were scattered throughout the parenchyma and were embedded in a partly necrotic and hemorrhagic matrix which contained free red cells and a considerable amount of bile-stained debris. The sinusoids and Kupffer cells were absent.

*Spleen.*—The trabeculae were increased in number and showed considerable hyalinization. The follicles were small and were characterized by an almost uniform involvement of the central arterioles by hyalinization of their walls, which were somewhat thickened, causing partial obliteration of the lumen in some areas. The intervening pulp was irregularly congested. The endothelial cells were increased in number. The cellular elements within the pulp meshes consisted mainly of round cells with occasional polymorphonuclears and some macrophages.

## COMMENT

*Etiology.*—There are two main factors to be considered in the etiology of acute yellow atrophy: the status of the liver cells and extrahepatic influences.

Acute yellow atrophy, according to numerous investigators, is the result of an infection or toxic factor on liver cells which previously have been (a) congenitally defective, (b) impaired by nutritional disturbances, or (c) depleted of glycogen content. The latter conception of the importance of carbohydrate metabolism is stressed by many.[2, 7]

The extrahepatic influences are (a) infections which reach the liver by way of the blood stream, bile ducts, or gastrointestinal tract and are due to streptococcus, smallpox virus, and other organisms; (b) toxic and poisonous substances, such as mushrooms, cinchophen, salvarsan, chloroform, etc.; and (c) chronic conditions, such as congenital or secondary syphilis and tuberculosis.

We shall limit our discussion to acute yellow atrophy due to influences in the first group.

Several authors feel that there is a common causal factor in the production of epidemic benign icterus (acute hepatic hepatitis) and acute yellow atrophy and point to the increasing frequency of both conditions in recent years as significant.[8]

Isolated instances of acute yellow atrophy have appeared during the course of an epidemic of catarrhal jaundice. Herlitz and Norlen[9] encountered one fatal case in an epidemic of 20 cases of jaundice, vomiting, and diarrhea. Their patient ran a mild course for eight days and on the ninth day developed an intense icterus and intestinal hemorrhages which proved fatal. Lenhartz[10] reports the case of a boy of 4 years of age who appeared to be ill with the same disease as others in the neighborhood. He developed convulsions and coma and died. Thomas[11] describes a case in a 7-year-old boy of acute yellow atrophy during an epidemic of icterus. Hirschberger[12] refers to a 7-year-old girl who fell ill during a mild epidemic of catarrhal jaundice and who died during the fourth week of her illness. She presented the usual picture of acute liver atrophy. Her brother was taken ill on the day of her death, ran a mild course, which was characterized by pain in the right hypochondrium, slight jaundice, hepatomegaly, and splenomegaly, and eventually recovered.

The occurrence of these cases has intrigued all students of this subject. Why should one or more children unexpectedly develop acute yellow atrophy and die while scores of others run a mild course and recover from what at the onset appeared to be a similar condition?

Several theories bearing on the interrelationship have been advanced but none is conclusive. The precipitating factor responsible for the conversion from an innocent to a fatal condition varies from emotional upset or dietary indiscretion to infections or toxic damage to the liver cells already depleted of glycogen.[13]

The answer to this question may furnish the solution of the general problem of acute liver atrophy as stated by Schminke[14] in 1924 when he wrote that, "We do not know as yet the reason why in one case there is a mild parenchymal damage with early restitution and integrum while in another there ensues severe tissue damage with signs of high-grade toxemia and rapid death as a result of liver insufficiency and in still other cases a cure is eventually established through reparative and regenerative processes."

*Pathology.*—The essential features of this disease are a rapid and marked reduction in size of a large, solid organ, an extensive necrosis, and the speedy absorption of much of the necrotic cellular debris in contrast with other forms of necrosis. The histologic picture varies with the amount of destruction and of repair. In rapidly fatal cases there is marked destruction of the liver cells, but there is insufficient time for the removal of the destroyed cells and their replacement by proliferative connective tissue or new hepatic cells. The color of the liver is predominantly yellow due to fatty degeneration of the liver cell and nucleus. In less rapid cases, areas of dark red color appear, the so-called red atrophy, as a result of hemorrhage and dilatation of the blood vessels and absorption of the fatty material and regeneration of the liver cells. Multiple nodular hyperplasia may be noted in the acute form as well as in the chronic. The microscopic picture is not uniform. Roman and Sherman[15] observed in their 8-month-old patient, who had been ill five days, a high degree of fatty degeneration with inflammatory infiltration of the portal spaces and an increase in the bile ducts. Lenhartz[10] considered his case one of acute yellow atrophy in spite of the absence of the usual signs of necrosis of acute atrophy. Our patient had a diffuse degenerative hepatitis with areas of regeneration in addition to the necrosis of acute yellow atrophy.

*Symptoms.*—The clinical course in children does not differ much from that observed in adults.

The disease is ushered in by symptoms similar to those of catarrhal jaundice, manifested by nausea, vomiting, abdominal pain, and jaundice which may be slight at the onset but more pronounced as the disease progresses. Icterus may be absent in acute fulminating cases.

The liver is temporarily enlarged at the onset but shrinks in size within a few days or a week. In some instances, this shrinkage of the liver may be the first sign of the disease. The spleen enlarges and the abdomen is distended because of an associated ascites. The stools are acholic or slightly clay colored and the urine is pigmented. Involvement of the skin consists of pruritus in the majority of instances and of petechial and purpuric spots in severe cases, associated with melena, hematemesis, and epistaxis.

Central nervous symptoms appear early in severe cases and include apathy, sleeplessness which may merge into a coma from which the patient may not awaken, restlessness, delirium, twitching of muscles, and, at times, a meningeal picture. The pulse is slow and the temperature not elevated.

The course of the disease lasts from a few days to a few weeks and even months, depending upon the severity, and may be divided into four stages: (1) an acute stage of one to five days; (2) a subacute stage of five days to three or four weeks; (3) a subchronic stage of four weeks to several months, and a chronic stage of months to years.[2, 4] Some claim that the majority of cases in children fall into the subacute and chronic stages and that mild cases are relatively frequent, but others feel that almost every case of true liver atrophy in children terminates fatally within several days to three weeks.

*Diagnosis.*—A diagnosis of acute yellow atrophy of the liver is made on the history, progressive jaundice, diminution of a previously enlarged liver, the appearance of cerebral symptoms, such as convulsions and coma, and the findings of laboratory evidence of hepatic insufficiency. These are a rising icterus index, an immediate strongly positive direct van den Bergh reaction, an increase in blood cholesterol with reversal of the ratio of free cholesterol to cholesterol esters, and the presence of leucine and tyrosine crystals in the urine. The presence of these cleavage products of the protein molecule is indicative of hepatic deficiency in the assimilation of protein and has been noted in acute yellow atrophy of the liver, erysipelas, enteric fever, leucemia, obscure febrile conditions, and even in proved instances of benign icterus. The presence of leucine and tyrosine crystals in the urine is confirmative of, but their absence is not prejudicial to, a diagnosis of acute yellow atrophy of the liver. They may be present in the liver and be absent in the urine.

Many consider the presence of a lipemia as presumptive evidence of liver disease, excluding the hypercholesterolemia found in hypothyroidism and nephrosis. The ratio of free cholesterol to cholesterol esters normally is 20 to 50 per cent of the former to 80 to 50 per cent of the latter. In any case associated with jaundice, any major deviation from or reversal of this ratio suggests a liver disturbance. This change in

cholesterol partition may take place before a marked increase in total cholesterol is noted in the blood, as was observed in our case.

A retrospective review and correlation of the clinical manifestations and laboratory findings in our case bear out the possible prognostic significance and value of the icterus index in acute yellow atrophy. The progressive elevation of the icterus index observed throughout the illness, although concomitant with the degree of intensity of the jaundice, preceded the abrupt change in the clinical picture. Several determinations obtained during the period of latency revealed such marked deviations from the normal as to indicate a more malignant condition than had been anticipated. A steadily rising icterus index in the presence of a persistent icterus predicates latent or potential liver pathology with an unfavorable or guarded prognosis.

Other tests which cannot be discussed in detail are glucose or galactose tolerance tests, phosphatase content of the blood, and the van den Bergh reaction.

Acute yellow atrophy is to be differentiated from epidemic benign icterus, congenital syphilis, icterus neonatorum gravis, poisoning from mushroom, salvarsan, cinchophen, and other toxic substances, and Weil's disease (epidemic jaundice).

Benign icterus in epidemic form or acute epidemic hepatitis has been observed in children and is characterized by a prodromal stage of one to seven days with vomiting, colic, diarrhea, and fever, which is followed by icterus, acholic stools, oliguria, and dark-colored urine. The liver is generally enlarged and sensitive; the spleen is also enlarged. The course is usually from several days to a few weeks and ends in recovery.[16]

Weil's disease is characterized by early fever, prostration, headache, myalgic pains, conjunctival congestion, jaundice, and a tendency to hemorrhage from the mucous membranes. The *Leptospira icterohemorrhagica* is found in the patient's blood in the early stages and in a guinea pig after injection of some of the patient's blood or of sediment from centrifuged urine obtained after the eighth day of illness.

*Prognosis.*—There is a difference of opinion as to the prognosis in children. Some authors feel that most of the cases are mild and recover and are mistaken for catarrhal jaundice or epidemic benign icterus (epidemic acute hepatitis). These are probably the cases which start as icterus simplex and show an incomplete picture of acute liver insufficiency. Once the complete syndrome is established (rapidly increasing jaundice, atrophy of a previously enlarged liver, and cerebral symptoms), then the prognosis is invariably fatal, with death occurring within a few days to several weeks. Some children may temporarily recover but soon suffer a relapse which terminates fatally. A small percentage of patients with completely established cases may run a chronic course with eventual recovery, nodular hyperplasia, or cirrhosis.

*Treatment.*—Therapy of acute yellow atrophy is generally unsatisfactory. The agent of choice is an adequate supply of carbohydrates in sufficient quantities to prevent depletion of the liver cells.

In experimentally produced necrosis, it has been shown that available carbohydrates and stored glycogen afford protection to the liver. Regeneration of the damaged liver cells continues at a more rapid rate following the administration of large amounts of carbohydrates either in the diet or parenterally.

Clinical therapy follows along the experimental lines and consists of the administration or ingestion of large amounts of sugar in the diet by the intravenous or subcutaneous injection of 5 to 10 per cent dextrose solution or the intravenous injection of 100 c.c. of a solution containing 20 to 30 per cent of dextrose and 10 to 15 units of insulin.

## SUMMARY

A fatal case of acute yellow atrophy of the liver occurring in a female child of 12 years is presented with autopsy findings. The experience in this case demonstrates the importance of repeated determinations of the icterus index, van den Bergh reaction, and blood cholesterol (total, free, and esters) in any case of liver disease, irrespective of the mildness of the clinical picture. A rising icterus index, an increase in intensity of the jaundice, and an increase in blood cholesterol content with a reversal of free cholesterol to esters are of grave prognostic significance. The presence of leucine and tyrosine crystals in the urine is confirmative of, but their absence is not prejudicial to, a diagnosis.

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# THE DIFFICULTY IN BEGINNING RESPIRATION SEEN IN INFANTS DELIVERED BY CESAREAN SECTION

## An Analysis of One Hundred Consecutive Cesarean Sections

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RENEWED interest in infants delivered by cesarean section may be of value because occasionally nature in her moments of abnormality reveals her secrets. The behavior of the newborn infant delivered by this method may furnish some glimpse of the inner mechanics of the start of respiration.

### CLINICAL STATISTICS

The last consecutive 100 infants delivered by cesarean section in St. Joseph's Infirmary have been studied carefully. These infants were delivered on a maternity service attended largely by obstetricians. In this group of newborn infants, there were fifty-two males and forty-eight females.

Table I

| NO. OF INFANTS | MALE | FEMALE |
|---|---|---|
| 100 | 52 | 48 |

Sixty-six per cent of these infants were the result of the first pregnancy, 26 per cent of the second pregnancy, 3 per cent of the third pregnancy, 1 per cent of the fourth pregnancy, and 4 per cent unknown.

Table II

| PREGNANCY | |
|---|---|
| First | 66 |
| Second | 26 |
| Third | 3 |
| Fourth | 1 |
| Unknown | 4 |

In this group of 100 infants, the great majority, 72, were delivered upon indications of fetal-maternal dystocia, contracted pelvis, elderly primipara, and previous sections, indications that were conducive to an essentially normal infant, being subjected to no trauma of birth or fetal asphyxia. Nine infants were subjected to possible intrauterine asphyxia as produced by placenta previa, placenta ablatio, and fetal distress from other causes. Ten were premature infants. The indications for cesarean section taken from the hospital records are given in Table III.

From the Pediatric Service of St. Joseph's Infirmary.
Read before the Harris County Medical Society, Sept. 3, 1941.

TABLE III

| | |
|---|---|
| Fetal-maternal dystocia | 27 |
| Contracted pelvis | 23 |
| Elderly primipara | 12 |
| Previous section | 6 |
| Pre-eclampsia | 8 |
| Nephritic toxemia | 4 |
| Placenta previa | 4 |
| Funnel pelvis | 4 |
| Placentae ablatio | 3 |
| Test of labor; no progress | 3 |
| Fetal distress | 2 |
| Cervical dystocia | 1 |
| Flat pelvis | 2 |
| Nephrosis | 1 |
| Dwarfism | 1 |

The largest number of the mothers of this group of infants were between the ages of 25 and 35 years. The age groups are given in Table IV.

TABLE IV

| AGES OF MOTHERS (YR.) | |
|---|---|
| 15 to 20 | 4 |
| 20 to 25 | 17 |
| 25 to 30 | 25 |
| 30 to 35 | 20 |
| 35 to 40 | 13 |
| Above 40 | 2 |
| Unknown | 19 |

Before delivery 51 per cent of the mothers of the infants of this series received no analgesic. The analgesics used in this series are given in Table V.

TABLE V

| | |
|---|---|
| None | 51 |
| Nembutal or seconal with pantopon | 19 |
| Nembutal alone | 17 |
| Pantopon and morphia | 8 |
| Amytal | 2 |
| Amytal with pantopon | 1 |
| Sodium luminal | 1 |
| Sodium bromide | 1 |

Cyclopropane was the anesthetic used in 69 of the mothers. In a number of instances the mothers received two different anesthetics at the time of cesarean section. The anesthetics are given in Table VI.

Of the 100 infants delivered by cesarean section, a large number, 42, required active resuscitation of some form. The division of these infants according to sex and compared to the number of infants requiring resuscitation in a consecutive series of 100 infants delivered normally in the same period is given in Table VII.

TABLE VI

| ANESTHETIC | |
|---|---|
| Cyclopropane | 69 |
| Nitrous oxide | 13 |
| Ether | 12 |
| Ethylene | 9 |
| Spinal | 1 |

TABLE VII

| NUMBER OF INFANTS REQUIRING RESUSCITATION | | MALE | FEMALE |
|---|---|---|---|
| 100 CESAREAN SECTIONS | 100 NORMAL DELIVERIES | | |
| 42 | 18 | 20 | 22 |
| | | 10 | 8 |

The ages of the mothers of the infants requiring resuscitation as compared to the ages of the mothers of the entire series are given in Table VIII. Infants of mothers in the age period of 25 to 30 years were somewhat more likely to require resuscitation than other age groups.

TABLE VIII

| AGES OF MOTHERS (YR.) | INFANTS REQUIRING RESUSCITATION (%) | ENTIRE SERIES (%) |
|---|---|---|
| 15 to 20 | 5 | 4 |
| 20 to 25 | 12 | 17 |
| 25 to 30 | 35 | 25 |
| 30 to 35 | 24 | 20 |
| 35 to 40 | 5 | 13 |
| Above 40 | | 2 |
| Unknown | 19 | 19 |

Infants of the second pregnancy for some reason showed a higher incidence requiring resuscitation. The number of the pregnancy of the group requiring resuscitation as compared to the number of the pregnancy of the entire series is given in Table IX.

TABLE IX

| PREGNANCY | 100 CESAREAN SECTIONS | 42 RESUSCITATION INFANTS |
|---|---|---|
| First | 66 | 60 |
| Second | 26 | 36 |
| Third | 3 | 2 |
| Fourth | 1 | 2 |
| Unknown | 4 | - |

In Table X the incidence of anesthetics used in the group requiring resuscitation is compared with that of the whole series. In this small series the incidence of use of cyclopropane was essentially the same in the entire series and the group requiring resuscitation. This is suggestive that the quantity of anesthetic in the cyclopropane group was not

an important factor in the need for resuscitation. Attention is directed to the high incidence of nitrous oxide and ether in the group offering difficulty in resuscitation.

TABLE X

| ANESTHETIC | INCIDENCE OF USE | |
|---|---|---|
| | ENTIRE SERIES (%) | RESUSCITATION INFANTS (%) |
| Cyclopropane | 69 | 62 |
| Nitrous oxide | 13 | 19 |
| Ether | 12 | 16 |
| Ethylene | 9 | 5 |
| Spinal | 1 | - |

Particularly interesting in this study is the careful scrutiny as to the analgesic received by the infants having difficulty in being resuscitated. The analgesics received in the entire series of 100 infants is contrasted in Table XI with those received by the infants requiring resuscitation. Attention is directed to the high incidence of infants requiring resuscitation whose mothers received nembutal and pantopon.

TABLE XI

| ANALGESIC | PERCENTAGE IN 100 CESAREAN SECTIONS | PERCENTAGE IN 42 RESUSCITATED INFANTS |
|---|---|---|
| None | 51 | 31 |
| Nembutal or seconal with pantopon | 19 | 36 |
| Nembutal alone | 17 | 22 |
| Pantopon | 8 | 7 |
| Amytal | 2 | - |
| Amytal with pantopon | 1 | 2 |
| Sodium luminal | 1 | 2 |
| Sodium bromide | 1 | - |

The weights of infants requiring resuscitation as compared to the weights of the entire group are given in Table XII.

TABLE XII

| WEIGHTS OF INFANTS | PERCENTAGE IN 100 CESAREAN SECTIONS | PERCENTAGE IN 42 RESUSCITATED INFANTS |
|---|---|---|
| Below 4 pounds | 1 | 2 |
| 4 to 5 pounds | 9 | 13 |
| 5 to 6 pounds | 15 | 16 |
| 6 to 7 pounds | 20 | 26 |
| 7 to 8 pounds | 24 | 21 |
| 8 to 9 pounds | 18 | 10½ |
| 9 to 10 pounds | 12 | 10½ |
| Unknown | 1 | 1 |

Weight losses of the infants for the first three days are given in Table XIII. As a rule, infants receiving no drugs lost the greatest amount, and infants receiving morphia lost the least.

The incidence of unusual symptoms as occurring in the newborn infants is given in Table XIV.

In this series 6 infants died. Five were female and 1 male. Three infants of these 6 were premature. Two of the mothers received morphia in some form. One mother received nitrous oxide and ether as an anesthetic. Four infants were the result of the second pregnancy and 2 of the first. These 6 case histories are reported briefly, and post-mortem findings are given when available.

TABLE XIII

| TYPE OF ANALGESIC | PERCENTAGE OF LOSS OF WEIGHT IN 100 CESAREAN SECTIONS | PERCENTAGE OF LOSS OF WEIGHT IN 42 RESUSCITATED INFANTS |
|---|---|---|
| None | 8 | 9 |
| Nembutal and luminal | 8 | 8 |
| Codeine, morphia, or pantopon | 6 | 5 |
| Nembutal and pantopon | 7 | 7 |
| Amytal and pantopon | 7 | 5 |

TABLE XIV

| SYMPTOMS | NUMBER CASES | PLACENTA PREVIA OR PLACENTA ABLATIO |
|---|---|---|
| Groaning | 9 | 3 |
| Cyanosis | 18 | 5 |
| Convulsions | 2 | |
| Vomiting | 2 | |
| Restlessness and irritability noted frequently | | |

CASE REPORTS

CASE 1.—Female, whose weight was 3 pounds, 2 ounces, was a second pregnancy, and the mother was 29 years of age. The mother received nembutal and pantopon before delivery; anesthetic, cyclopropane. Infant had artificial respiration, mouth to mouth. She grunted constantly, had frequent cyanotic spells, and died after fourteen hours.

CASE 2.—Female whose weight was 6 pounds, 6 ounces, was the second pregnancy, and the mother was 23 years of age. The mother received nembutal before delivery; anesthetic, nitrous oxide and ether. At delivery the infant was pale, cyanotic, and required oxygen. Respirations ceased several times. She grunted constantly, had frequent cyanotic spells, and died after twenty-four hours. Briefly, post-mortem examination showed a cerebral edema with atelectasis of the lungs.

CASE 3.—Female whose weight was 4 pounds, 8 ounces, was the first pregnancy, and the mother was 25 years of age. The mother received no analgesic and the anesthetic was cyclopropane. Note on the delivery chart showed the infant to be depressed. She grunted constantly and considerable mucus was aspirated. There were frequent periods of cyanosis. She died after eighteen hours.

CASE 4.—Female whose weight was 4 pounds, 13 ounces, was the second pregnancy, and the mother was 35 years of age. This child was a twin. No note was made of any analgesic. Cyclopropane and ether were used as an anesthetic. At delivery the infant was weak, cyanotic, and grunted constantly. She died after thirty-six hours. Her sister who preceded her at delivery was normal. Post-mortem examination showed edema of the brain with a large hemorrhage in the left frontal area.

CASE 5.—Female, whose weight was 6 pounds, 10 ounces, was the second pregnancy. The age of the mother was unknown. The mother received nembutal before delivery. The anesthetic was cyclopropane. The infant required oxygen for resuscitation, grunted considerably, and had frequent attacks of cyanosis. She lived twelve days. The pediatric diagnosis was prematurity and atelectasis.

CASE 6.—Male, whose weight was 5 pounds, 8 ounces, was the first pregnancy, and the age of the mother was unknown. The mother received pantopon before delivery. The anesthetic used was ether. Delivery by cesarean section was because of placenta ablatio. The infant was cyanotic at birth, listless, and grunted a great deal. He lived fifteen hours. Post-mortem examination showed atelectasis, edema of the brain and throughout the body, and a hemorrhage in the posterior fossa of the brain.

In this series of 100 consecutive cesarean sections there were only 3 infants who had a trial of labor, and none of the 3 were asphyxiated. During the preceding two years there were 48 infants delivered by cesarean section whose mothers had a test of labor. In this group 25 per cent had difficulty in beginning respiration. This group of infants was influenced by several factors other than the test of labor. Only one was a premature infant and 80 per cent were above 7 pounds in weight. This increase in average size would tend to lessen the incidence of asphyxia. On the other hand, 70 per cent had an analgesic, and 50 per cent had morphia in some form. Cyclopropane was used as an anesthetic in 42 per cent and nitrous oxide and ether in 46 per cent, which would give a higher incidence of asphyxia than occurred in the large group of 100 consecutive cases. It is believed that the reduction in incidence of difficulty in beginning respiration in this group of infants having a test of labor is significant, particularly since there were strong factors operating that would tend to increase the incidence of asphyxia.

The question might justifiably be raised as to whether these infants were asphyxiated, narcotized, or anesthetized. From a study of the histories it can be stated that they had difficulty in beginning respiration only, and the word asphyxia is used in this paper in that sense.

## DISCUSSION

Stander[1] and Holt and Howland[2] make no mention of increased difficulty in beginning respiration of infants delivered by cesarean section. Eliminating the premature infants and the infants exposed to intrauterine asphyxia in this series having difficulty in respiration, there is still a much greater percentage; namely, 32 per cent who received absolutely no trauma at birth as compared to a percentage of 18 per cent[3] who developed difficulty in respiration after a normal delivery during which the infants were subjected to active labor, a greater incidence of associated trauma at birth, as passing through the birth canal and use of forceps, and a higher incidence of analgesics of 76 per cent.[3]

The clinical findings in this series of cesarean sections suggest that there is some factor missing in infants delivered by this method that

conditions an infant more easily to start his respiration. The possibility that this factor is that of alternate pressure and release of pressure as a result of uterine contractions with the onset of labor is suggested. This factor probably acts in two different ways. The first method and probably most important in which increased uterine pressure affects the fetus is the mechanically compressing of the placenta, forcing more blood into the fetus. The results of this additional forced blood in the fetus is seen in the initial slowing of the fetal heart with uterine contractions. With the passing of the uterine contraction, the heart rate increases, indicating that the infant is then in some oxygen want. Another clinical observation suggesting that the fetus has sufficient oxygen with uterine contractions is the fact that the fetus with beginning labor pains and at the height of uterine contraction is usually quiet. Occasionally after the labor pain has passed and the fetal heart rate increases, the fetus will become active and move vigorously. This alternate forced oxygenation and decreased oxygenation probably affects the respiratory center and conditions the infant to respond quickly to changes that are conducive to beginning respiration. The infant delivered without his respiratory center being prepared for changes that stimulate the center apparently responds more sluggishly to these changes upon delivery. By acting in this manner the uterine musculature functions as a necessary accessory muscle to initiate respiration.

Secondly, the alternate pressure and release of pressure upon the fetus directly, and particularly the chest wall and lungs as the infant leaves the birth canal may be another important factor in beginning respiration.

It is generally recognized that analgesics play a very important part in the production of asphyxia of the newborn infant. Cole[4] pointed out that asphyxia was directly proportional to the amount of analgesic, kind of analgesic, and the time before delivery that the mother received the analgesic. Recently Arnold[5] clearly demonstrated that there is danger associated to the infant with the use of any drug, even in small quantities. As with Cole, he further stresses the fact that the use of morphia alone or in combination with other drugs is associated with a great deal of danger to the infant and provides an unsatisfactory relief of pain to the mother. The danger of analgesics to the infant is clearly shown in this group of infants having asphyxia.

Rosenfeld and Snyder[6] stress the dangers of certain anesthetics to the fetus. They point out the risks of ether and nitrous oxide, particularly when the percentage of oxygen is less than 15 per cent. In this series the dangers of these two anesthetics is again demonstrated.

## SUMMARY

A series of 100 consecutive newborn infants delivered by cesarean section has been carefully studied.

In this series there has been a high incidence of difficulty in beginning respiration compared to a corresponding group of infants delivered normally during the same period.

It is believed that one factor in this high incidence of difficulty in beginning respiration may be the result of the lack of the conditioning of the respiratory center of the fetus by uterine contractions. One method of this conditioning possibly consists in the alternate forcing and drawing of blood from the fetal circulation by compressing the placenta.

Another possible factor in this high incidence of difficulty in beginning respiration seen in cesarean section is the lack of compression of the fetus by the uterus with release of that pressure when the infant leaves the birth canal.

In view of the above it is believed further that the uterine musculature can function as an important accessory muscle to the fetus to initiate prompt respiration.

The dangerous effects of analgesics, particularly morphia and its derivatives, and of some anesthetics upon the newborn infant delivered by cesarean section is again demonstrated.

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# UNILATERAL PARALYSIS OF THE DIAPHRAGM WITHOUT INVOLVEMENT OF THE BRACHIAL PLEXUS

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ONE-SIDED paralysis of the diaphragm in infancy due to injury of the phrenic nerve is unusual except when associated with brachial plexus damage.

While the literature concerning phrenic nerve palsy is not extensive, there are several interesting reports. Naunyn,[1] in 1902, was the first to record a case of unilateral palsy of the phrenic nerve associated with injury to the brachial plexus. Kafferath,[2] in 1921, recognized brachial plexus and phrenic nerve paralysis at birth and emphasized the value of the fluoroscope in detecting the characteristic paradoxical movement of the diaphragm. Epstein,[3] in reporting a series of similar cases in 1927, concluded that "injury to the phrenic nerve without concurrent involvement of the brachial plexus has never been cited in the literature, nor can one conceive of such a phenomenon." Tyson and Bowman,[4] in 1933, reviewed the literature up to that time, reporting eight cases of paralysis of the diaphragm in the newborn infant, and adding five cases of their own. In one of these, Dyson's[5] patient, the phrenic nerve injury was caused by accidental laceration of the neck at the time of delivery. With the exception of two, all cases reported by Tyson and Bowman showed onset of symptoms of diaphragmatic paralysis within the first twenty-four hours of life. In these two, symptoms were noted on the third and thirteenth days respectively. The authors concluded that injury to the phrenic nerve is usually of obstetric origin, due in most cases to the use of forceps during delivery. Excluding Dyson's case, all other cases except one were associated with brachial plexus paralysis on the same side. In this exception Tyson and Bowman thought it possible that pressure of the forceps blade on Erb's point during delivery might have produced phrenic paralysis without damage to the brachial plexus, admitting, however, that some type of cerebral injury had also to be considered as a possible etiologic factor. No reference was made to post-mortem findings of the phrenic nerve or diaphragm in their single fatal case.

Rupilius,[6] 1933 and 1934, reported a case of right phrenic nerve paralysis accompanying brachial paralysis and wry neck. In this case the symptoms, due to phrenic nerve paralysis, did not occur until the sixth week of life and then rather suddenly, associated with an acute respiratory infection. He believes that nerve injuries of this type may

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be prenatal in origin, induced by the position of the fetus in utero during the later months of pregnancy, particularly the position of the head and shoulders. According to Rupilius, compression of the brachial plexus and phrenic nerve between the acromial portion of the clavicle and the curved portion of the inner side of the first rib against the transverse processes of the fifth and sixth cervical vertebrae could produce such a nerve injury. He cites Kehrer's experiments with animals and necropsy material, which seem to lend support to his contention. He also reviews the report of Erlacher (1920), who believed that brachial injury occurred prenatally.

Sebolovitch,[7] in 1936 and 1937, discussed phrenic nerve paralysis and divided the cases into two classes: (1) Phrenic nerve paralysis associated with brachial paralysis, usually right-sided; (2) so-called isolated phrenic nerve paralysis, unassociated with brachial palsy. He reviewed nine cases of the first type and five of the second.

As a sixth example of the latter type, Kottgen,[8] 1938, reported a case of right-sided phrenic nerve paralysis in a premature infant of seven months' gestation, a second child of healthy parents, born in a difficult manual delivery from transverse position without the aid of forceps. Rapid breathing was first noted at the age of 4 weeks when the patient developed an acute respiratory infection. The diagnosis of paralysis of the right side of the diaphragm was made without any evidence of other nerve injury. The injury was thought to have occurred during the process of birth.

## CASE REPORT

T. B., white male, aged 6 months, was first admitted to St. Louis Children's Hospital on Aug. 12, 1939, because of failure to gain weight, dry cough, occasional projectile vomiting, and difficult respiration over a period of two months. He was a second child, born at home without medical attendance, following an unexpectedly short labor. No abnormalities were noted during the neonatal period. At no time was there any evidence of brachial plexus injury. The birth weight was 7 pounds, and he had developed well on an evaporated milk formula supplemented with orange juice and cod-liver oil. His weight was 12 pounds, 12 ounces at the age of 3¾ months. The mother noticed that at the age of four months he had stopped gaining weight and had developed a dry, hacking cough, which did not seem to be associated with fever. The cough became progressively worse and seriously interfered with feeding. He would often cough during the feeding and vomit. About this time it was noted by the family physician that the breathing was rapid and labored. During the week prior to admittance the respiratory distress became more marked. An x-ray film of the chest revealed a dense shadow on the right side. A thoracentesis was performed, but only a small amount of bloody material was obtained. The patient was then referred for further study.

The patient appeared to be chronically ill. Weight was 12½ pounds. The respirations, however, were extremely rapid, 70 to 90 per minute, regular, and moderately deep. There was an occasional irritative cough. The breathing was largely thoracic. There was no cyanosis. The tissues generally were soft and flabby. There was a pigmented area 1 by 2 cm. in size on the right arm, but no subcutaneous nodules were noted.

Examination of the chest showed a slight lag on the right. The percussion note was flat over the entire lower portion of the right chest. Above the area of flatness there was resonance; just below, tympany. The entire left side was normal. The breath sounds were completely absent over the lower right chest. No râles were heard. The mediastinum was definitely shifted to the left. The heart sounds were normal. The abdomen was scaphoid. The liver edge could not be felt, nor could the spleen or kidneys. Except for a mild pharyngitis, nothing else of note was found.

Fluoroscopic examination revealed a dense shadow in the lower part of the right lung which appeared to be the liver (Fig. 1). The heart and mediastinum were pushed over to the left. As the left leaf descended, the right ascended, and vice versa. The excursion of the left leaf was about 5 to 6 cm.; that of the right, 1 cm.

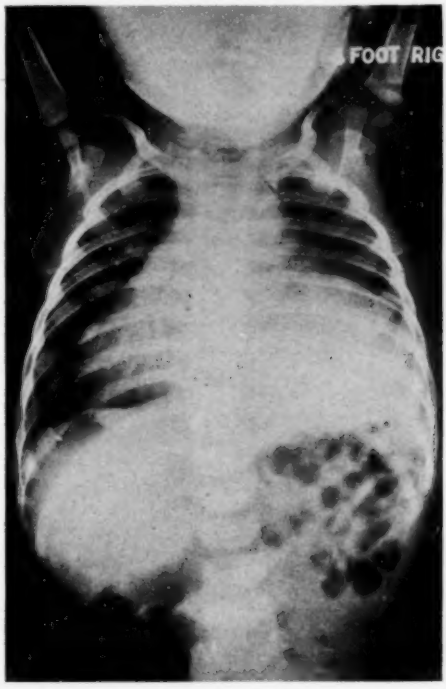



Fig. 1.—X-ray of chest.

A barium meal revealed a greatly distended stomach. No barium entered the thoracic cavity. Hospital stay of five days was uneventful except for vomiting on two occasions.

At home he continued to do very well for four days. He ate well, gained weight, and seemed quite fit. The fifth day he seemed ill and on the day following became much worse and was readmitted to the hospital.

At this time he was limp, was moderately cyanotic, and had a temperature of 38° C. The respirations were 80 per minute and labored, all of the accessory muscles being drawn into play in the respiratory effort. Intravenous dextrose and subcutaneous lactate-Ringer's solution were given, and he was placed in an oxygen tent. Temporarily he responded very well to these measures with improved color and

a slower respiratory rate. At 8:00 A.M. on the day following admission he suddenly became cyanotic, respirations became irregular, pulse imperceptible, and he soon died.

## AUTOPSY FINDINGS

The autopsy was performed by Dr. Margaret G. Smith, Department of Pathology, Washington University. Permission granted was for chest and abdomen only. Inspection showed skin normal except for a light brown mark, measuring about 2 by 1 cm., on the anterior surface of the right upper arm. The positive autopsy findings were as follows: The right lobe of the liver extended high into the thoracic cage; the diaphragm was intact over it, but completely relaxed, and gave the impression of having a large right leaf. The right thoracic cavity was greatly diminished in size by the high right leaf of the diaphragm. The phrenic nerve on each side appeared grossly normal. The one on the right side was dissected high into the neck without revealing changes in adjacent tissue. Its course seemed normal. In view of the pigmented area on the skin, a careful search was made for nodules along these nerves. None was found. The heart position was shifted slightly to the left. The right lung was partially atelectatic. Its lower lobe was uniformly purplish in color, and seemed to contain little air. The middle and upper lobes were not remarkable. The left lung showed some superficial areas of atelectasis. While the lung on this side almost completely filled the pleural cavity, there was no overdistention, as might be expected in view of the marked atelectasis on the right.

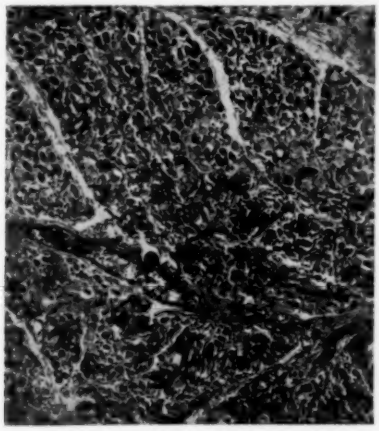
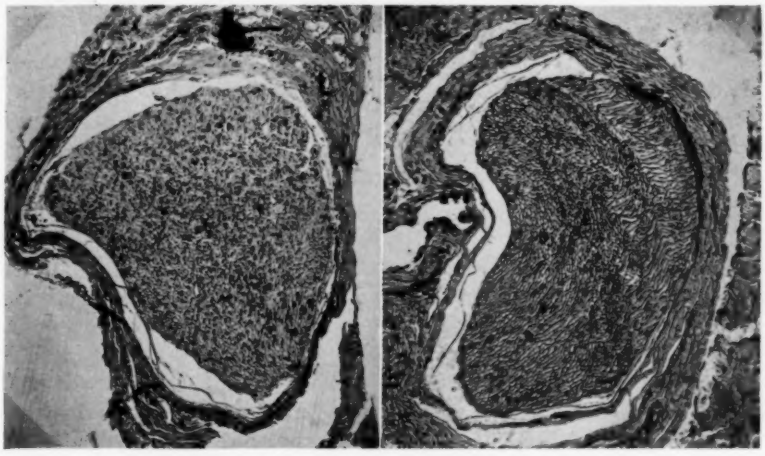


Fig. 2.—Section from right leaf of diaphragm. Hematoxylin-eosin stain ×75.

Microscopic examination revealed the following: Section of the lower lobe of the right lung showed a uniform atelectasis with no inflammatory reaction in the pleura. In some of the partially collapsed alveoli mononuclear leucocytes appeared. Section of the left lung revealed nothing unusual. A section of the left leaf of the diaphragm appeared normal. A section from the right side showed a degenerative change in the muscle. Some groups of fibers were small and atrophic. In other muscle bundles, while the fibers ranged around normal size, some were hyalinized, and others stained very lightly with eosin. These latter especially varied in size. No inflammatory process was evident in the muscle. In the subserous tissue on both pleural and peritoneal sides of the diaphragm a small number of mononuclear cells were concentrated about the smaller vessels. A very thin film of fibrin appeared along the pleural surface (see Fig. 2). Sections were taken through both the right

and left phrenic nerves, including the surrounding pericardium. There was no inflammatory reaction about either nerve and no detectable difference in the size of the two nerves. That on the left appeared normal. The right nerve trunk was much more cellular, with marked increase of nuclei. Masson stain revealed striking increase in the amount of blue-staining fibrillary substance. Only a few orange-stained nerve axones could be distinguished (Fig. 3). Scharlach R stain on a frozen section of this abnormal nerve disclosed no fat droplets.



*A.* *B.*

Fig. 3.—Cross section of phrenic nerves. *A*, right (patient's); *B*, left (patient's). Masson's stain ×35.

## DISCUSSION

Several phases of this subject are of particular interest. Etiology in phrenic nerve injury is obscure. Since phrenic nerve damage is often accompanied by brachial plexus injury on the same side, most observers have explained the nerve damage by attributing it to obstetric manipulation during delivery, and specifically, in many instances, to the application of obstetric forceps. However, when phrenic nerve injury occurs, which is unassociated with brachial plexus damage, the explanation is not so simple. Tyson and Bowman,[4] who had difficulty in explaining their single case of isolated phrenic nerve injury, suggested pressure of the forceps blade on Erb's point. Such localized injury is difficult to understand when one considers the relative size of the forceps blade. In the light of such cases as the present one, the contention of Rupilius and Erlacher offers a more plausible explanation. They believe that injury of the brachial plexus and phrenic nerve occurs prenatally due to compression of the nerves between the acromial end of the clavicle, inner surface of the first rib, and the transverse processes of the fifth and sixth cervical vertebrae. The phrenic nerve arises from the third and fourth cervical segments in close association with the brachial plexus,

which arises from the fifth, sixth, seventh, and eighth cervical and first thoracic. The phrenic nerve leaves the brachial plexus and passes down the sheath of the anterior scalenius muscle between the subclavicular artery and veins, goes behind the clavicle, and thence courses down the mediastinum to the diaphragm on each side. There is a considerable portion of the nerve in the neck that is separate from the brachial plexus and may, therefore, be subject to compression injury, as explained above, without involving the brachial plexus. Separate compression of the phrenic nerve by this mechanism seems a much more logical explanation. Dissection and careful study of the neck in several newborn infants lend support to the above possibility. The compression injury is due apparently to the position of the fetus in utero during the last months of pregnancy. The shoulder presumably is pressed toward the head, which causes compression of the nerve. Another possibility is damage to the cervical cord. Since in the case reported here we did not have permission for detailed dissection of the cervical cord, no definite conclusion can be drawn. However, the infant was the second born, was delivered with no difficulty and without the use of the obstetric forceps. Consequently, prenatal injury to the phrenic nerve seems to be the best explanation of the findings. The possibility that both phrenic and brachial injuries had been present and that by the time of our examination the brachial palsy had entirely disappeared does not seem likely, since none of the infant's relatives, including a physician, had noted any arm paralysis at any time. Birth injury has been suggested to explain paralysis of the phrenic nerve in central nervous system damage, but in our case there was no evidence of any cerebral symptoms.

In our patient the onset of respiratory symptoms occurred late; i.e., at 4 months of age. Symptoms usually occur at birth or soon after, although there are several cases reported with onset of symptoms at the ages of 3 days, 13 days, 4 weeks, and 6 weeks. A respiratory infection usually initiates distress by overtaxing the already impaired breathing apparatus.

Prominent physical signs are rapid, often irregular, thoracic type of breathing, definite lag on the affected side, lack of the respiratory bulge in the epigastrium on the involved side, and shift of the mediastinum toward the uninvolved side. Examination of the chest reveals an impaired percussion note and absence of breath sounds at the base of the lung on the involved side. Because of the paralysis of the diaphragm on the right side, as in this case, the liver extends up into the thorax, thereby compressing the lung. X-ray films of the chest show this relationship very well (see Fig. 1), but fluoroscopic examination gives absolute proof of the condition. The paradoxical or "see-saw" movement of the diaphragm is diagnostic. The paralyzed side ascends during inspiration and descends during expiration. The uninvolved side pursues the usual course.

Several conditions are often confused with paralysis of the diaphragm. Empyema, atelectasis of the lung, diaphragmatic hernia, pneumonia, cerebral injury, and congenital heart disease must be considered. The diagnosis, however, is not difficult, especially with the aid of fluoroscopic examination. Treatment is symptomatic. Prevention of respiratory infections is important since poorly aerated lungs are fertile ground for bacterial invasion.

The pathologic findings are of particular interest in this case, since, in so far as can be determined, this is the first case in which sections of the phrenic nerve were studied and reported.

In addition to the pathologic changes in the phrenic nerve, there was degeneration of the muscle fibers of the diaphragm on the right side.

## SUMMARY AND CONCLUSIONS

A case of so-called "isolated" phrenic nerve injury with paralysis of the diaphragm in a 6-month-old infant with onset of symptoms at 4 months of age is reported. This is the seventh such case recorded in the literature.

Etiology of the paralysis is most likely prenatal compression injury of the phrenic nerve, due to position of the fetus in utero during the last months of pregnancy, rather than obstetric manipulation.

The pathologic findings of note are degeneration of the phrenic nerve and degeneration of the muscle fibers of the diaphragm on the involved side.

Diagnosis of the condition is discussed and the value of fluoroscopic examination emphasized.

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# SELF-SELECTION OF DIETS

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FOR many years I have been interested in the spontaneous or self-regulatory activities of animals. During the past six years this interest was focused largely on studies of self-regulatory activities concerned with dietary selections. From these latter studies, many of which were made in collaboration with Dr. Emmett Holt, we are gradually uncovering the factors involved in the origin of appetites and aversions for different foodstuffs and non-nutritional or poisonous substances. We believe that all of our results thus far obtained, not only from these self-regulatory studies concerned with dietary needs, but also from self-regulatory studies concerned with other needs, may be understood in terms of a biologic concept first announced in 1859 by the great French physiologist, Claude Bernard.[1] This is the concept of the maintenance of a constant internal environment. Bernard showed that in animals the body fluids which constitute the internal environment must have a fairly constant mineral content, acid-base relationship, temperature, etc., and that even small deviations from the fixed levels might threaten life. In normal individuals, the body meets such threats with mechanisms which serve to restore the various functions to their fixed levels. Thus, when the body is exposed to a cold external environment which threatens to lower body temperature, decreased sweating reduces heat loss, while burning of fat, shivering, etc., increase heat production. Many other well-known instances of self-regulation could be cited. Haldane stated that Bernard's concept of a constant internal environment was the most important advance in modern medicine.[2] Cannon greatly elaborated this concept and spoke of a steady state or homeostasis. The results of his studies are summarized in his well-known book, "The Wisdom of the Body."[3]

Bernard and Cannon dealt largely with the physiologic regulators, responses of individual organs or systems, which serve to maintain a constant internal environment. From our behavior studies, made chiefly in relation to the endocrine glands, we have learned that the organism itself, the total organism, may also play an important part.

In the intact organism these total responses are likely to be overlooked or regarded simply as reactions to various external stimuli. It was not until we were able to eliminate the physiologic regulators, or part responses, under experimental conditions that we obtained a clear view of the total organism responses which serve to maintain a constant internal environment. Most of the examples that will be offered come from the

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studies on the self-selection of diets. However, in order to establish the broad biologic basis for this concept, examples will be offered from studies on the regulation of other functions.

The first example concerns the maintenance of a constant water balance. In the intact organism we know that the regulation of the water balance depends largely on the antidiuretic secretion from the posterior lobe of the pituitary gland. When the organism is threatened with dehydration, the gland secretes more antidiuretic hormone. As a result, the kidney excretes less urine; and consequently, less water is lost from the body. When the body has an oversupply of water, the gland secretes less antidiuretic hormone, the kidney excretes more urine, and more water is lost. Surgical removal of the posterior lobe thus eliminates the most important part of the physiologic means of regulating the internal water balance. When not given access to water, animals lost as much as one-sixth of their body weight in less than eight hours after posterior lobectomy and, as a result, died much sooner than normal animals deprived of water. If given access to water, they drank very large amounts and, as a result, kept themselves alive and in good health indefinitely. Some of the rats drank almost twice their weight in water every day. In this condition we must regard the high water intake, the polydipsia, not as a pathologic symptom, but as an effort made by the whole organism to maintain a constant internal environment. Many clinicians and experimental workers still regard the polydipsia of diabetes insipidus as an isolated phenomenon which results from a brain injury and bears no relation to the total organism. It is clear, however, that after the physiologic means of regulating water metabolism has been removed, the organism itself makes an effort to maintain a constant internal environment by drinking large amounts of water.[4]

The next example concerns the maintenance of a constant body temperature. In the intact organism we know that the regulation of body temperature depends to a large extent on the secretions from the pituitary and thyroid glands. After removal of either one of these glands, the rate of metabolism decreases and body temperature falls. If such an animal is kept even in only a slightly cooled room, its body temperature will soon fall below the level compatible with life. Given the opportunity, such an animal will make an effort to conserve heat and to maintain normal body temperature by covering itself with large amounts of nesting material. This we were able to demonstrate experimentally and with quantitative methods. The cages used for these experiments contained a food cup, a water bottle, and a roll of soft tissue paper, ½ an inch wide and 500 feet long. The end of the roll of paper was introduced through a glass tube which projected about three inches into the cage. The paper hung freely from the end of this tube and within easy reach of the rat. All of the paper pulled into the cage was removed each day at noon. It was found that normal rats, males and females alike, will build nests

every day, even though each day all of the nest paper is taken away. The amount of paper used increases in cold temperatures and decreases in warm temperatures. After removal of the pituitary or thyroid glands, the rats built very large nests, even at ordinary room temperature. Some of them used the entire roll each day.[5]

Thus, we have here another instance in which, after the physiologic means of maintaining a constant internal environment ceases to function, the animal itself makes an effort to attain this end.

The third example concerns the maintenance of constant mineral, carbohydrate, and fat levels in the blood stream. It is a well-known fact that the adrenal glands regulate sodium metabolism. In rats, when these glands are removed, sodium leaves the body in the urine in excessively large amounts, upsetting the internal sodium balance so much that death follows in a few days. When sodium chloride is supplied either in the food or by injection as rapidly as it leaves the body, these animals can be kept alive and free from symptoms of insufficiency. At this point our research began. We were interested to know whether, when adrenalectomized rats are given access to sodium chloride in a container separate from their food, they will voluntarily take sufficiently large amounts to keep themselves alive and free from symptoms of insufficiency. For this purpose we used very simple cages which contained a food cup and two graduated inverted bottles, one filled with tap water, the other with a 3 per cent solution of sodium chloride. The food contained no added sodium chloride. Records were made daily of the intake from the two bottles. Adrenalectomy was not performed until the intake from each bottle had reached a fairly constant level. Almost immediately after operation, in some instances within a few hours, the rats began to drink more of the sodium chloride solution; and after several weeks they drank ten to fifteen times as much per day as they had before. As a result, they survived without loss of weight or symptoms of insufficiency. The significance of these findings is emphasized by the fact that 100 per cent of the adrenalectomized rats die when kept on a sodium-chloride-free diet, while 100 per cent of those on such a diet with access to sodium chloride solution survive. Adrenal implants made to the anterior chamber of the eye cause the sodium chloride appetite to decrease to its normal level again. If given access to a number of different electrolytes, the adrenalectomized rats regularly choose sodium solutions.[6] We have found recently that they show a decreased appetite for the carbohydrate dextrose. This agrees with the current view that adrenalectomized animals have a reduced ability to absorb carbohydrate. When treated with desoxycorticosterone, the adrenalectomized rats lost their sodium chloride appetite and regained their dextrose appetite. Cortical extract produced similar changes in appetite, except that it affected primarily the dextrose appetite while the desoxycorticosterone had a greater effect on the sodium chloride appetite.[7]

Similar observations were made on parathyroidectomized rats. Biochemical and clinical studies have established the fact that the parathyroid glands regulate calcium and phosphorus metabolism. After removal of these glands, the calcium level of the blood falls, and the phosphorus level rises. Rats quickly develop tetany and usually die within a few days. We were interested to know whether, after the physiologic means of regulating the calcium metabolism had been removed, the rats themselves would make an effort to maintain a constant calcium balance. The same cages were used as in the experiments with adrenalectomized rats. Each rat had access to a calcium-free diet and two bottles, one filled with water, the other with a 2.4 per cent solution of calcium lactate. Parathyroidectomy quite regularly increased the calcium lactate intake far above the normal levels. Some of the rats drank twenty times as much of the calcium lactate solution as they had before. Parathyroid implants made to the anterior chamber of the eye caused the calcium appetite to decrease to its normal level again. These rats showed an increased appetite for other calcium salts, the acetate, nitrate, and gluconate, but not for the salts of other metals, with the exception of strontium and magnesium, both of which are closely related to calcium and both of which have ameliorative effects on clinical parathyroid tetany.[8]

Similar observations have been made on the regulation of the carbohydrate and fat metabolism of pancreatectomized rats. Biochemical and clinical studies have shown that the pancreatic secretion of insulin plays an important part in the metabolism of carbohydrates. Without insulin the blood sugar increases, the weight decreases, and polyuria and polydipsia set in. Rats made diabetic by pancreatectomy were given access to a fat (olive oil), a carbohydrate (sucrose), and a protein (casein), and various minerals and vitamins in separate containers. On the selections made from this assortment of substances, stock rats show normal growth and reproduction. The pancreatectomized rats, which on the standard McCollum diet had for several months shown all the symptoms of diabetes, were put into multiple food choice cages with access to fifteen substances in separate containers. These rats ingested large amounts of the olive oil and little or none of the sucrose and took large amounts of casein and yeast. As a result of these choices, the rats gained weight, lost their polydipsia and polyuria, and their blood sugar decreased. When they were returned to the McCollum diet, which forced them to take the fat, carbohydrate, and protein in certain fixed proportions, all of the diabetic symptoms promptly reappeared.[9]

The results of these experiments described above establish the fact that, after the physiologic means of maintaining a constant internal environment have been removed, the organism itself makes an effort to attain this end. We may conclude either that the behavior factors take over only after the physiologic factors have been eliminated or that in

the intact organism they both must function more or less at the same time. In all probability the latter conclusion gives the most accurate description of this situation.

That the behavior factors play an important part in the intact organism is shown by nutritional experiments made on normal rats. We found that these rats made advantageous selections from as many as fifteen different substances, all offered in purified (or nearly purified) form, one fat, one protein, one carbohydrate, five minerals, members of the vitamin B complex, and vitamins A and D.[10] On their selections the rats grew as well as on the McCollum diet although they ate from 15 to 40 per cent less food per day as measured in grams.

This knowledge of the close relationship between dietary selections made by animals and their internal needs offers us a new tool for the investigation of many phases of nutrition. Had this method been available, we could have established many years ago, long before the advent of modern biochemical methods, that the adrenal glands are concerned with the regulation of sodium metabolism. It would only have been necessary to place an adrenalectomized rat in a cage containing a variety of mineral solutions in different containers. Likewise, we could have discovered the calcium regulatory function of the parathyroids, etc. This method applied to the study of vitamin B deficient rats has already uncovered needs not previously detected by biochemical methods.

The question arises: How are the rats able to make such wise and advantageous dietary selections? There are two obvious possibilities: (1) The rats sample the different foods and eat the one which makes them feel better (in other words, the dietary selections are made on the basis of previous experience or conditioning); and (2) they depend primarily on taste and are independent of experience. Thus, according to the latter information, it may be said that in an adrenalectomized rat all the tissues of the body have a sodium deficiency, including the taste buds of the tongue. When sodium chloride comes in contact with the tongue in adrenalectomized rats, it produces quite different reactions than in a normal animal. It may even have a different taste. Evidence for this view comes from the following experiment in which normal rats were offered a choice between distilled water and varying concentrations of sodium chloride solution. Normal rats first recognized a difference between the water and the salt solution in a concentration of 1 part of salt to 2,000 parts of water. Under the same circumstances adrenalectomized rats recognized the difference in a concentration of 1 part of salt to 33,000 parts of water.

Further evidence for this view came from the observation that adrenalectomized rats in which the taste nerves had been sectioned no longer showed an increased appetite for salt and, as a result, died within a few days.

In the normal intact organism we do not know the relative importance of the roles played by the physiologic and behavior factors. It is conceivable that the relationship might be something like this. For example, an animal with defective adrenal cortex, and hence lacking in the sodium regulatory hormone, may compensate for the abnormal salt loss by increasing its salt intake. On the other hand, in an animal living in a region which offers little or no salt, the adrenals might become overactive and thus conserve salt, or in animals which are forced to eat exceedingly large amounts of salt the adrenals might atrophy and thus allow the elimination of more salt.

Thus far we have not made many comparable observations under experimental conditions on human beings. We have, however, observed many instances of salt craving in patients with Addison's disease and in other conditions involving a partial or total destruction of the adrenal cortex. One such patient, a 3½-year-old boy, who was brought to the hospital for precocious sex development, was described in collaboration with Dr. Lawson Wilkins.[11] While under observation primarily for the endocrine studies of his sex development, this boy was put on a regular ward diet which included the normal amount of salt. He died unexpectedly in seven days. At autopsy it was found that the greatly hypertrophied sex zone of the adrenals had obliterated the cortex. Just before leaving for home the mother remarked that the boy had shown a marked craving for salt. In response to a few simple questions we received an eight-page letter which is a most interesting behavior document.

During the first year the child had presented a serious feeding problem until it was found by chance that he liked salty crackers and later plain salt. On the local doctor's advice he was permitted all the salt he wanted. He ate it literally by the handful, enjoying it as other children do sugar. When at the age of 3½ he was brought to the hospital and placed on an ordinary diet without access to extra salt, he died very unexpectedly. He had kept himself alive previous to this time exactly the way adrenalectomized rats do. We have records of patients with Addison's disease who crave salty soups, salty ham, and one patient who regularly robbed the juice from the sauerkraut barrel. A patient who came to the hospital last fall took about half a glass of salt with his tomato juice and put salt on grapefruit, oranges, and lemons.

Undoubtedly, most of the instances of peculiar appetites will be found to have dietary significance.

Dr. Clara Davis demonstrated some years ago that young children, given free access to a variety of natural foods, will make selections which result in normal growth and development.[12] This same observation had been made previously at agricultural stations in feeding swine.[13] However, when natural foods are used, the results are confused by the numerous ingredients; and it cannot be determined which one of the

various ingredients is sought. It is now possible to offer selections made from strictly purified substances, even the crystalline members of the vitamin B complex.

That human beings often make faulty dietary choices may be explained in part by parental guidance and by the effects of advertisement. Often, when a child expresses a great appetite for certain substances, he is told by his parents that he must not eat them; equally often he is told to eat things which are very distasteful to him. He quickly learns to distrust his own appetite; and when he comes under the influence of advertisements, he falls prey to them.

Actual defects in the gustatory apparatus, the tongue, the taste nerves, or the cortical areas of the brain, may also account for faulty choices. Salmon and Blakeslee found that about 3 out of 100 individuals are at least partly taste blind to a bitter substance, phenylthiocarbamide.[14] Their lack of ability to taste this substance is inherited on a Mendelian basis as a recessive. We have found individuals who could not recognize a 10 per cent solution of sucrose.

## SUMMARY

The results of these studies have shown (1) that a close relationship exists between appetite and dietary needs; (2) that animals make beneficial selections from purified substances, even better than from natural foods; (3) that we have a new tool for the investigation of a variety of nutritional problems (up to the present the results have been largely confirmatory of biochemical studies; in the future we hope with this method actually to be able to point the way to new relationships); and (4) that all of the dietary self-selection activities may be regarded as total organism responses by means of which the organism maintains a constant internal environment.

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# PHYSICAL EXPRESSION OF PSYCHOGENIC DISTURBANCE IN CHILDREN

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PHYSICIANS have always encountered individuals who have referred their apparently inexplicable complaints to some part of the body. Formerly it was felt that with improved methods of pathologic and biochemical examination, all of these organic or structural manifestations would be fully understood, as, witness the Virchow period of disease consideration, based essentially on finding the etiology of some pathologic change. This process of trying to find an anatomic point of localization was first applied to mental disease.

Following the work of Freud, who contributed the psychoanalytic approach to the understanding of the individual, a great interest arose in the psychic origin of disease. With hysteria it was realized that so dramatic a manifestation as the paralysis of a limb could arise from emotional conflicts. This paralysis in turn might even lead to degenerative changes in the extremity. Thus, at the present time the emotional processes of the individual are considered to be interrelated with his bodily processes, each influencing the other. Alexander[1] states "Once again, the patient as a human being with his worries, fears, hopes, and despairs, as an indivisible whole and not only as the bearer of organs, of a diseased liver or stomach, is becoming the legitimate object of medical interest."

Some of the earlier investigations relative to the relationship of the emotions and bodily change were carried out by Cannon.[2, 3] He emphasized the importance of the sympathetic nervous system in relation to the adrenals and the role of the thalamus in controlling emotions. Since then the concept of "psychosomatic" medicine has been developed to indicate that underlying emotional conflicts may find their outlets in bodily manifestations; that there is no separation of mind and body.

Gillespie[4] has referred to certain characteristics of the psychopathology of childhood; namely, the tremendous influence of the environment upon the child's mental processes, the plasticity of the latter, and the prominence of symptoms in children centering principally round their egoistic, self-preservative or self-assertive striving. When basic frustrations occur, difficulties are likely to arise.

Jordan[5] has referred to the basic needs of every child as three in number: (1) the need for security, (2) the need for affection and understanding, and (3) the need for achievement and recognition.

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The neuroses are said to occupy more than one-half the chronic illnesses of childhood.[6] Emotional concerns and anxieties may find their outlets not only as classical psychoneuroses, but may find their expression in organic or physical manifestations, either with or without structural change. A neurotic tendency may be noted early in life. A common illustration is the "hypertonic infant," with symptoms of constant crying, vomiting, diarrhea, sleeplessness, but with generally good nutrition yet inability to gain apace.

Acting upon the inherited constitution of the child is the experience acquired through daily contact with home and school life. These experiences may operate as exciting factors on the child. Daily repetition of these excitants may condition the child to a definite form of behavior. The experiments of Pavlov[7] have aided in understanding this conditioning process. In the first, the serving of food to a dog simultaneously with the ringing of a gong produced a flow of saliva and gastric juice. After constant repetition the stimulus of the sound of the bell alone caused the same response. Then a reconditioning process was carried out. When a cat was exhibited along with the food and the bell, the attention of the dog was distracted, and no salivation or gastric juice was produced. Finally the sound of the bell alone produced no salivation. Similarly, the teacher or parent may exert an effect on the child, resulting in a certain type of behavior. Mere association without the presence of teacher or parent may reproduce the behavior pattern. Other modes of interpretation may be utilized to understand the child's symptoms. The physical disorder may serve as an outlet for the fears or frustrations of the child. The "conversion hysteria" of Freud,[8] and the "bodily protest" of Richards[9] are examples.

Jealousy as a factor is linked with the position of the child in the family. Levy[10] has referred to the importance to a 3-year-old child of a new arrival. The competition for mother love, the hatred unleashed against, first, the baby, then the mother, may lead to symptoms of an organic neurosis.

The therapeutic approach must be based on finding the etiologic factors on the hypothesis that an emotional conflict or psychic trauma has been the underlying factor in producing the organic symptoms.

We may demonstrate the expression of the somatic manifestations of psychic disturbances through the records of children seen at the child guidance clinic or on the pediatric wards of the Long Island College Hospital.

CASE 1.—J. M., aged 6 years, was bitten by a mad dog two months before admission to the hospital. The dog was shot and a diagnosis of rabies was made by the board of health. Following the bite, a course of antirabic treatment was begun. On one occasion, two weeks before entering the hospital, the child screamed and fainted. He was unconscious for from two to three minutes. Then he acted normally except for profuse spitting. His appetite was good throughout this time. He went to a movie on the day of admission to the hospital and returned home

shaking all over. Suddenly he shrieked, clutched his throat, could not swallow, and said he was going to die. The admission diagnosis was rabies. However, the symptoms cleared within a few hours. The physical and laboratory examinations were normal.

The children in the street had constantly tormented him about going mad and about choking because he had been bitten by a suspicious dog. The child's confidence was restored and no further difficulty followed. He made an uneventful recovery.

CASE 2.—J. F., a girl of 14 years, had not been attending school for the past five years because of recurrent chorea (Sydenham). The first attack occurred within a month of the time the maternal grandmother came to live with the family because of the death of her husband. After a period of hospitalization for chorea, the child was sent to a convalescent home. After returning to her own home, her father died, which event appeared to precipitate a second attack. The patient refused hospitalization at this time, saying to her mother, "You put my father away and now you want to put me away too." This statement was made because the patient had become aware of parental friction. However, the child finally went to the hospital, where her condition was considered possibly to be a conversion hysteria of the hyperkinetic type. During the hospital stay she would see her father's image on the ceilings and walls; she felt that she had not been nice enough to him during the last week of his life. If she happened to be cheerful, she would become moody and depressed when visited by her mother. There was present a low-grade chronic chorea which was obviously influenced by the charged atmosphere at home. The mother was emotionally unstable. The child was self-centered and also very labile emotionally. An effort is being made to treat her at home, though a change of environment may have to be considered. Such subacute types of chorea as this involve both organic and psychologic factors, and from both standpoints progress is slow and uncertain.

CASE 3.—F. L., a 13-year-old boy, was admitted to the hospital because of twitching and tremor of the arms and fingers. Two weeks before, he had had severe palpitation of the heart and awoke during the night saying he was going to die. At this time he had a marked tachycardia. Following this episode he stayed away from home all of one night. Four days before hospitalization, twitching of both arms began, finally ending in a coarse tremor which involved the whole body. The child had a heart rate of 180 and some rigidity of the arms while walking. He had had measles and chicken pox, but no encephalitic manifestations complicated these illnesses. The boy was superior mentally. He volunteered that the whole family was "nervous." One maternal aunt had toxic goiter. Another aunt had a severe tic to which the child constantly alluded. "One aunt went blind for no reason at all." The patient was very talkative, had frequent crying spells, and insisted that he did not want to go home. He wished to go to the country.

The question of encephalitis arose, but this diagnosis was finally abandoned in favor of the diagnosis of a neurosis manifested by way of the neuromuscular and circulatory systems.

Interviews with the parents revealed the fact that the father was 52 years old and the mother 31. This was his second marriage. The first ended in divorce. On the mother's part the marriage was loveless. She had been intrigued by his wealth. In recent years he had lost most of his money while she had come into an inheritance. She was now having an affair with another married man. The child was aware of the marital difficulties and had witnessed frequent quarrels.

There were enough elements of anxiety, fear, worry, emotional insecurity, and lack of attention to produce the behavior which followed. Therapy consisted in explaining the underlying etiologic factors to the parents. The mother took the

boy away with her for a week, and they spent all their time together. The boy was reassured, received recognition, and had a greater sense of security. Upon his return to his home, a change in milieu was recommended. In view of the desire of the boy to go to the country, he was sent to a farm for the summer. In the fall he was sent to a boarding school for a year, during which time he was constantly visited by both parents together. Following this year the boy remained at home. He was physically well. The parents have continued to live together and have cooperated to avoid open display of their marital incompatibility. The boy is 17 now, is graduating from high school, and has had no recurrence of his neurotic behavior.

CASE 4.—A., aged 11 years, was referred because she cleared her throat so frequently that it became annoying and irritating to others about her. In addition she had a feeding problem according to her parents who considered her to be nervous and underweight because of it. The patient was first beaten and forcibly compelled to eat, whereupon she would cry hysterically when food was served. The child was put to bed at eleven at night. The mother was nervous and the father was ill with chronic arthritis. Upon examination the child was somewhat underweight but was otherwise normal. The problem was one of emotional difficulties, in which both parents were ill, financially insecure, and were projecting their lack of security on to the child. These difficulties have begun to affect the other child of 7 years in a similar manner.

The movement on the part of the child to clear her throat was unconscious and compulsive. It is possibly a replacement of an inner feeling of discomfort or emotional tension. The child knows that she must eat in order to be healthy; yet she is conscious of the lack of food in the house. Therapy must be directed toward the elimination of the conflict between these two ideas.

Ties are sometimes manifested in the form of eye blinking, head jerking, and twitching of the arms and legs. In all such instances, our effort is directed at relief of the emotional disturbances suspected to be the cause of their development. No direct attempt is made to affect the motor movements, and, as a further protection, the parents and teachers must not urge the child to cease the movement. The usual analysis of the day's routine is made to avoid overfatigue.

CASE 5.—G. F. was admitted to the pediatric wards of the Long Island College Hospital with symptoms suggestive of brain tumor. For the past two months she had had headaches and markedly decreasing vision with blurring. Examination revealed diplopia plus contraction of the visual field. The fundi were negative. The general physical examination disclosed nothing abnormal. On the third day of hospitalization the patient's visual defects cleared suddenly and completely. There were no more headaches nor any other untoward symptoms.

These pertinent facts concerning the home were elicited from the mother. She felt uncomfortable because she had but one child. This, she said, was due to the fact that their income did not permit more children and that the patient was an "expensive child."

Plans for treatment must be based on the reasons that the patient's eyes failed her. Since most of the activities urged upon her by the mother, and apparently complied with by the child, were those in which the eyes are needed, as in sewing, reading, doing puzzles, and desk-play activities, her loss of vision might have been a hidden protest. Since her eyes had failed her, she had a reason to discontinue her busy round of work at home and leave her mother for the hospital.

Furthermore, the child had a friend who had a "nervous breakdown," and her eyes had failed. Her intimate identification with that friend may have given rise

to the suggestion which caused her own symptoms to take the form of failure of vision. Individuals often choose friends like themselves, and this is particularly true of neurotic individuals.

Both parents appeared to be anxious, talkative, and emotionally tense. They appeared baffled when the situation was explained to them and relieved to learn that the child did not have a tumor.

This patient had an hysterical amblyopia established by the elimination of organic disease. The hysteric is not conscious of the psychogenic origin of his somatic disease. Wolff and Lachman[11] reported two cases in which emotional conflicts were engendered through loss of affection and resulted in hysterical blindness. Suggestion as a therapeutic agent has been utilized in the form of sham irradiation by x-ray, galvanic current, and operations, but these are doubtful practices. Sometimes it is of value to ignore the matter temporarily. The home and school should be carefully surveyed as possible irritants. The physician may help a great deal by a display of friendly interest and understanding.

CASE 6.—F. R. was treated for asthma in the allergy clinic since his twelfth year. Injections of "cold vaccine" were regularly employed without improvement. At 13½ years of age he was referred to the child guidance clinic for study because of his failure to respond to therapy. His physical examination disclosed no abnormality. His I.Q. was 86 by the Stanford Binet test. He was restless, fidgety, and emotionally unstable. Study of his home revealed constant conflict with his father who beat him. The patient said these conflicts were begun by his father in order to bring the mother into an argument. Since an uncle entered the house, the boy stated that the father and mother quarreled constantly. The father was unemployed and did not want to work. The only time the patient had been happy was when he went to the country.

On two subsequent occasions dramatic attacks occurred. In one instance, the boy rang the fire alarm, and when the engines arrived, he stated that he called them because he was going to have an asthmatic attack. On another occasion he came back to the allergy clinic stating that if he did not get an injection, he would develop an immediate seizure.

As in the above instance, it is often difficult to decide when true asthma exists, and if present, how much of the symptomatology is on an allergic basis and how much on a psychic basis. Rogerson[12] found that symptomatology referable to asthma disappeared when the child was placed in a convalescent home, only to reappear when he returned to his own home. No allergic causes were discovered in this case and a psychic reason was suspected. He reported that these children showed marked anxiety with insecurity and inhibited aggressiveness. Similarly, the parents were quite anxious and overprotective. Of 25 patients, 10 were cured and 8 were helped through a psychotherapeutic approach, directed particularly toward the parents. McDermott and Cobb[13] reported on a psychiatric survey of 50 cases of bronchial asthma in adults. Thirty gave clear stories of a psychologic precipitation or aggravation of their attacks. Of these, 20 referred to their first attacks as being emotionally

precipitated. Only 20 per cent of the "emotional group" were benefited by somatic therapy, whereas 54 per cent of the "nonemotional group" were benefited.

The major manifestation of psychogenic bladder disturbance is the presence of nocturnal enuresis. Excluding those for which there is an organic cause, this group represents a large portion of the cases in any children's clinic. Much has been written concerning the subject. Schwartz[14] has presented in great detail the relationship of the psychic processes and bladder function. He poses the question as to why these children urinate at all during the night. Furthermore, the fact that the amount of urine is normal and that the reflex irritability of the bladder functions normally during the day time suggests the operation of psychic causes. Attempts have been made to classify these cases. Pototsky[15] grouped them into neuropaths, psychopaths, and mentally deficients. Behm[16] refers to them as degenerates, thick-skinned, and excited. Immaturity is present in these children. In others there is a poor capacity for training and carelessness concerning the formation of regular habits. Other factors, e.g., the lack of facilities, such as outdoor toilets, must be considered. In one of our children the cause lay in a spite factor. The child lived with foster parents. She resented the foster mother and in subsequent interviews with the child we were able to elicit the information that the nocturnal enuresis was deliberate to promote extra work for the foster mother.

CASE 7.—H. B. was referred because of a history of periodic attacks of diarrhea of two years' duration. His most recent attack had lasted eight days. A tentative diagnosis of gastroenteritis, possibly on an allergic basis, was made. After proctoscopic and x-ray examinations were made, the mother was told that there was nothing organically wrong with the child and to bring him to our clinic.

The patient was an 8½-year-old boy. He lived with his parents and a 15-year-old brother. During the past few years this family suffered severe financial reverses. In order to reduce living expenses, they were forced for a period of time to live in the same house with the patient's maternal grandmother. About a month before the onset of the present illness, the family moved to one of the new housing projects and set up their own household again.

Shortly after the family moved to the housing project, the patient was questioned about his religion by a gang of boys and suffered several severe beatings as a result. The patient is described by his mother as an unaggressive child who has never been able to fight back in any situation. After one or two beatings by this gang he was approached by another group who asked him the same question. This time he stated that he was one of them, and thus escaped another beating. Then he hurried home to his mother in a great state of panic and conflict because of what he had done. Diarrhea followed. As the mother related the incident to the social worker, it was quite clear that she, too, was upset by this denial of his race, but she told her son that it was justifiable as a means of self-defense.

When we interviewed the mother, she was able to recall other instances in which the patient had suffered from diarrhea following a traumatic experience.

In this instance we made contact with the school to get the cooperation of the authorities in handling the gang problem. Our further efforts were directed toward building up the child's self-confidence. The mother was informed as to the psycho-

logic implications involved in the production of the child's diarrhea. The housing project has an organized play group and the patient was introduced to the circle. There have been no further attacks of diarrhea since the advent of therapy.

## COMMENT

There has been presented for discussion a group of children who came for the relief of symptoms of a somatic nature for which no organic cause could be assigned. Rather, the explanation was to be sought in some environmental factor, such as the home, school, or neighborhood, which had acted upon the hereditary background of the child. The psychogenic disorder transpired through a sense of insecurity, and in many instances, anxiety, because of parental maladjustment. In other instances, fear, and frustrations through intellectual inadequacy were important factors. Emotional conflicts aroused by doubts as to what was proper occurred in others; these were particularly fruitful sources for hysterical manifestations.

In treating these children it is obvious that detailed attention must be given to the everyday experiences of the child. The physician has the opportunity to learn the situation in the home. He can rule out or discover all the organic causes for the complaints which the child presents. He can, with proper effort, evaluate the psychogenic factors associated with the illness, and, through the confidence reposed in him by parents and child, help to modify these factors and so relieve the tensions and emotional difficulties present. Since many of these problems occur early in the child's life, it is hoped that awareness and elimination of them will help to avoid the development of the full-blown neuroses and psychoses of later life.

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# American Academy of Pediatrics

## Proceedings

### ELEVENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

BOSTON, MASS.—OCT. 8-11, 1941

### Round Table Discussion on Whooping Cough

Chairman: J. M. Lewis, M.D., New York, N. Y.
Associates: Pearl L. Kendrick,* Sc.D., Grand Rapids, Mich.
John J. Miller, Jr., M.D., San Francisco, Calif.
Secretaries: Benjamin W. Carey, M.D., Detroit, Mich.
Matthew Lewison, M.D., Chicago, Ill.

**Discussion Opened by**
**Pearl L. Kendrick, Sc.D., Grand Rapids**

Let us look first at some basic information which we have gained about pertussis through bacteriologic and immunologic methods and then consider the practical implications. Quite naturally we go back to the demonstration and cultivation of the etiologic agent by Bordet and Gengou in 1906. Some years ago there was a period when a few authors cast doubt upon the bacteriologic etiology of pertussis and leaned toward the virus theory. The findings with respect to the Bordet-Gengou bacillus, or *Hemophilus pertussis*, however, have had ample confirmation.

As we study the papers of Bordet and his co-workers, we are impressed with the wide range of their observations. During the twenty years following their early reports, little was added to their findings, and recent work is really an extension and application of their discoveries. In his early report on the etiologic agent, Bordet expressed the hope that serum therapy and active immunization might find a place in the control of whooping cough. A few years later he reported an endotoxin and discussed the possibilities of a pertussis antitoxin, although he was unable to demonstrate it. Also he observed that pertussis cultures grown on laboratory media sometimes changed in their characteristics. This important observation was later expanded by Leslie and Gardner and various others and, in the light of more recent investigation of microbic dissociation in relation to antigenicity, helps to explain many of the divergent results reported in active immunization against pertussis.

*The Period of Infectivity.*—Studies of the etiologic agent have given us considerable information about the period of infectivity during an attack of pertussis. We may bring to mind the results of cough plate examinations in terms of the week of disease during which the isolations of *H. pertussis* were made. The reports of various authors indicate that *H. pertussis* can be isolated in a large percentage of instances during the first three weeks of disease, most often during the first. There is a sharp drop in the number of isolations during the fourth week and only an occasional positive result after the fifth week. These findings give experimental basis for emphasis upon the early stages of disease in the effort to prevent the spread of infection.

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*Organisms Antigenically Related to H. Pertussis.*—Respiratory disease clinically indistinguishable from pertussis sometimes is associated with organisms other than *H. pertussis* but antigenically is related to it. An attack of whooping cough which was shown by careful bacteriologic study to be associated with *Brucella bronchiseptica* was reported by Dr. J. Howard Brown of Baltimore. The isolation of parapertussis organisms by Eldering and Kendrick from patients with clinical whooping cough has been confirmed by various workers. More than fifty such cultures have been isolated in Michigan, and they have been reported in many other areas, including New York, California, Kentucky, Maryland, Illinois, and Mexico. These attacks of parapertussis in general are milder than true pertussis. Just how frequently they occur cannot be judged by the meager data available. The three organisms, *H. pertussis*, parapertussis bacilli, and *Br. bronchiseptica*, have been shown by Eldering and Kendrick to be closely related antigenically.

In relation to this group of cultures, the recent studies of Evans and his coworkers in England have particular interest. They have reported similar toxins for the three organisms and neutralization of all three toxins by *H. pertussis* antitoxin. Some practical implications of these bacteriologic observations will be referred to later.

*Immunologic Response to the Etiologic Agent.*—By immunologic procedures something has been learned about the response of the patient to the etiologic agent and its products. Various workers have demonstrated that specific opsonins, complement-fixing antibodies, and agglutinins are produced in response to either pertussis infection or pertussis vaccine injections.

The opsonocytophagic test has given much information in the hands of several workers. It is based on the fact that pertussis organisms mixed with blood containing specific opsonins are phagocytized by neutrophiles. In several reported series of observations, the highest opsonic titers have been found approximately two months after completion of immunization or after onset of a pertussis attack. In evaluating the results of any immunologic test, individual variation must be taken into consideration, both as to quantitative response and the time at which the optimum response occurs. The results of opsonic tests in 545 children in a Grand Rapids immunization series before completion of a course of injections with pertussis vaccine, and in 311 following the injections, illustrate the response to the vaccine. In comparison with insignificant reactions before vaccination, 86.8 per cent gave reactions which we consider significantly strong four and one-half to five and one-half months after immunization. Approximately a year following vaccination, 77.7 per cent of the children were still giving good reactions.

In this same immunization series the results of complement fixation gave a similar picture. In tests five to eight months after immunization, 89.9 per cent of the children gave positive reactions. It may be noted that the various results in the literature on complement fixation are not comparable because of the difference in antigen as well as in technique. These factors are receiving greater attention, and with better and standardized procedure we may expect to obtain more information.

Considerable work has been done with agglutination tests and various modifications in technique have been suggested. In general, agglutination tests in susceptible children are either negative or of low titer. The results after immunization are illustrated in some tests of children in a recent immunization series in Grand Rapids. Of 62 children tested six to fifteen months following immunization, 5 were negative in a dilution of 1:10, 9 had a titer of 1:10, and 48 had titers which ranged from 1:20 to 1:750. In general, in a group of vaccinated children, opsonic, complement fixation, and agglutination tests will be found significantly strong in approximately the same percentage.

*Bacteriologic and Immunologic Procedures Applied to Diagnosis.*—From the brief survey we have made of present information related to the etiologic agent in pertussis and its stimulation of immunity responses, we turn to the practical prob-

lems of diagnosis and prevention of the disease. For the diagnosis of pertussis, in which characteristic symptoms of whooping and vomiting are already present, laboratory procedures may not seem necessary. Their particular use is in early diagnosis and in atypical attacks. After the disease is well established the lymphocyte count and serologic procedures are of value, but in the earlier stages, the most helpful single diagnostic aid is the isolation of *H. pertussis*. With suitable technique this can be done from a sputum specimen by means of a cough plate or by the nasopharyngeal swab method suggested by Bradford, in which a small, flexible swab is introduced through the nares. Most of the reported success has been with the cough plate method of Mauritzen, which has been used in Copenhagen since 1916 and by many workers in the United States and England. Droplets of sputum from the trachea or bronchial passages are coughed onto a Bordet-Gengou plate, which is then incubated and examined at intervals for several days.

While there are certain difficulties involved in obtaining a properly inoculated plate, and the period of two to four days required for diagnosis is longer than might be wished, the method has proved efficient and practicable in many trials and is being used in various centers. It is unfortunate that the necessary facilities for the method are not more widely available.

*Some Bacteriologic and Immunologic Problems Related to Preventive Measures.*—While earlier and better diagnosis and more adequate isolation of the patient in the infective stages of the disease would be a long step in the direction of pertussis control, it is not sufficient. Real control of a disease like pertussis can be brought about only through specific preventive measures. This brings us to a consideration of certain bacteriologic and immunologic problems connected with these specific measures.

With the isolation of the etiologic agent, active and passive immunization against pertussis seemed almost within grasp. Some success with pertussis vaccine was reported but under conditions difficult to evaluate. The lack of convincing evidence and the discouraging results of some workers led to practical discontinuance, for a period, of efforts in the direction of immunization. Studies in bacterial variation and its effect upon antigenicity, however, in conjunction with the previously mentioned observations on dissociation of pertussis cultures, offered a possible explanation of the divergent results. Also, vaccines were found in use which showed no activity when tested for agglutinability with a smooth strain antiserum or for production of agglutinins in animals. These findings made it reasonable to doubt the efficacy of such products and gave direction to a reinvestigation of the question of pertussis immunization in controlled studies in which every precaution was taken to use a vaccine containing only active strains of pertussis. The results of a number of field studies afford convincing evidence for specific prevention of pertussis. It is recognized, however, that production of the vaccine used must have strict supervision. The cultures used must be active antigenic strains, as judged by bacteriologic and serologic tests. The final product must be so standardized that the dosage can be judged with some degree of accuracy, and it must be shown to be antigenic by suitable tests. The usual sterility and safety tests are assumed.

The lowered incidence of pertussis in vaccinated study groups in comparison with unvaccinated control groups is supported by immunologic studies. Extensive observations of vaccinated children by such means as the opsonocytophagic test have shown a marked response on the part of approximately 80 per cent of the children injected with active vaccine, a percentage in surprising agreement with the figures given by several workers for protection.

As the prevention of pertussis in a large percentage of injected children becomes firmly established, emphasis in pertussis studies is shifting to the type of vaccine and dosage. Immunologic study of the response to different products and different modes of administration already is yielding important information, espe-

cially with regard to dosage. There has been a tendency arbitrarily to increase the total dosage as an answer to occasional failures in protection. Concentrated suspensions, some containing up to 40 billion organisms per cubic centimeter, are now available to meet the demand for a high total dosage in relatively small volume. The question of optimum total dosage should be examined critically and an effort directed toward finding the lower limits of the quantity required for immunization of most children. Equal consideration should be given to the injection schedule. It may well be that the protection conferred by a relatively smaller total dosage given over a longer period of time will be found as good as by the larger quantity over a shorter period.

There is under study now in Grand Rapids a dosage schedule in which a total of 30 billion organisms is given in three injections, with one week between the first and second injections and four weeks between the second and third injections. In one series, an alum-precipitated pertussis vaccine has been used with this schedule in comparison with standard vaccine in the same dosage, and in another series combined diphtheria toxoid and pertussis vaccine is under investigation. Serologic studies of the children suggest as good response to this smaller dosage over a period of five weeks as to our previously reported dosage of 70 billion organisms given over a period of three weeks. The preliminary tabulations related to protection in these study series are in line with the serologic findings. All this suggests that studies directed toward the form of antigen and schedule of administration can be expected to yield significant information.

Another phase of the immunization problem about which we need more definite information is the duration of immunity and the related question of the role of the secondary stimulus. These questions cannot be answered by field studies alone. We need the help of immunologic studies as well. In a recent paper by Rambar and associates, a very rapid rise in opsonocytophagic reaction was noted following a secondary stimulus two years after the initial course of injections. More studies of this kind are needed. In the meantime, until more experimental data are available as a basis for action, it would seem reasonable to consider reimmunization of the child before he starts to school; perhaps also under known epidemic conditions, if his immunization series was completed more than two years previously. Limited experience suggests that a relatively small dose, perhaps 5 billion organisms, would provide an adequate secondary stimulus.

There is not time to discuss the problems associated with passive immunization. Suffice it to say that several workers have had encouraging results with hyperimmune sera, particularly when used for prevention of pertussis in exposed young infants. Cooperative clinical and immunologic studies should be pushed forward in this field.

*Promising Investigations of Unsolved Problems.*—Various studies are in progress in different parts of the world which may be the basis of better immunizing procedures in pertussis. In the early part of the discussion, Bordet's observation on endotoxin was mentioned. Bordet could not demonstrate that the toxic material he studied was antigenic, and most workers agreed with Bordet that there appeared to be little use for the toxin of *H. pertussis* in specific immunization. Some recent work of several authors, however, such as Evan's in England, seems to indicate that with proper technical procedure, an antitoxin may be produced against the toxin. This immediately raises the question of what part such toxin and antitoxin might play as immunizing agents. More work is required to determine whether protection is conferred by the toxin. A report on the use of toxoid has been made by Joslin in Baltimore. If it should be found that these toxic products confer protection, it would still be necessary to determine whether the protection is as good as that following the use of whole organisms.

Another promising line of investigation is the study of chemical fractions. Eldering has shown that polysaccharides from *H. pertussis* and the related species,

*Br. bronchiseptica* and the parapertussis bacillus, confer protection on mice against subsequent infection with these organisms. Of particular interest was the high degree of protection against *H. pertussis* infection in mice previously injected with the bronchiseptica polysaccharide.

Both the studies of toxin and chemical fractions of *H. pertussis* provide a hopeful approach to the problem of optimum antigen and also to the unsolved problem of the skin test as a measure of immunity. A reliable skin test would provide a most useful tool and deserves thorough investigation.

*Closing Comment.*—We have made an outline survey of information gained by the procedures of bacteriology and immunology; we have followed their application to diagnosis and preventive measures and to fundamental investigations which offer hope for the future. We have seen some accomplishment which lends encouragement; and we have recognized large gaps in our information, which emphasize the need for more intensive work.

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## The Diagnosis and Treatment of Whooping Cough*

John J. Miller, Jr., M.D., San Francisco

*Diagnosis.*—The clinical diagnosis of typical whooping cough in the paroxysmal stage is obvious. The clinical diagnosis of early preparoxysmal whooping cough or of atypical pertussis (whooping cough is here a misnomer) is quite impossible. Of course a history of exposure helps a good deal but in my experience the blood count does not. As a matter of practice, diagnosis of early whooping cough or atypical pertussis is not entirely essential to good management of the patient's case because there is no sure specific treatment. The doctor's reputation is more likely to be hurt than is the patient when the proper diagnosis is not made. The coughing child plays with his cousin and the cousin gets typical whooping cough.

I want then to discuss the means available to protect our collective reputations in diagnosing atypical pertussis and preparoxysmal whooping cough.

The bacteriologic test is the sole recourse available. Recently Bradford, Slavin, and Brooks[1, 2] have made a significant practical contribution to the isolation of *H. pertussis*. They take nasopharyngeal cultures by passing a very small wire applicator tipped with cotton through a nostril. The swab is then sent to the bacteriologist who streaks Bordet-Gengou medium. In the outpatient clinic at Stanford School of Medicine and in private practice, this procedure has been found to be superior to the cough plate technique. If both cough plates and swabs are taken, even better results will be obtained. Both of these techniques permit the diagnosis of pertussis in the catarrhal stage. In fact, the earlier the test is done, if one thinks of it, the more likely will *H. pertussis* be isolated. This is evident from Tables I and II.

*From the Department of Pediatrics, Stanford University School of Medicine.

TABLE I

210 TESTS ON 152 CASES IN WHICH BOTH COUGH PLATE AND SWAB WERE USED

| WEEK OF DISEASE | BOTH PLATE + SWAB + | PLATE + SWAB − | SWAB + PLATE − | BOTH PLATE − SWAB − | TOTAL | % + BY SWAB | % + BY PLATE | % + BY BOTH |
|---|---|---|---|---|---|---|---|---|
| First | 26 | 6 | 13 | 10 | 55 | 71 | 60 | 82 |
| Second | 21 | 4 | 19 | 20 | 64 | 63 | 39 | 69 |
| Third | 4 | 4 | 11 | 20 | 39 | 38 | 20 | 49 |
| Fourth | 7 | 3 | 3 | 9 | 22 | 45 | 45 | 58 |
| Fifth | | 1 | 4 | 9 | 14 | | | |
| Sixth | | | | 6 | 6 | | | |
| Seventh | | 1 | | 8 | 9 | | | |
| Eighth | | | | 1 | 1 | | | |
| Total | 58 | 19 | 50 | 83 | 210 | 51 | 37 | 60 |

TABLE II

RESULTS OF 154 CASES STUDIED

| | BOTH PLATE + SWAB + | PLATE + SWAB − | SWAB + PLATE − | BOTH NEGATIVE | TOTAL | TOTAL SWAB + | TOTAL PLATE − |
|---|---|---|---|---|---|---|---|
| Number of cases | 60 | 15 | 38 | 41 | 154 | 98 | 75 |
| Per cent of total cases | 39 | 10 | 25 | 27 | 73+ | 64 | 49 |
| Per cent of + cases | 53 | 13 | 34 | | | 87 | 66 |

I am not proud of these results, though I may mention that the swabs and plates were taken by many different individuals. Dr. Sauer and Dr. Kendrick did much better with cough plates alone. However, I wish to point out that the taking of cough plates and their examination require more skill than the swab procedure. The latter is simpler to obtain and the growth of the specific organism is usually heavier.

The application of this procedure to the practice of pediatrics depends to a great extent on training bacteriologic technicians in the culture and identification of *H. pertussis*. In only a few places is this organism studied in routine courses in diagnostic bacteriology. I believe we should urge our schools to teach this practical procedure.

I have been interested in the bacteriology of whooping cough for the past eight years. By doing cough plates (and recently nasopharyngeal swabs) on the children with coughs, I have found that atypical cases of pertussis are very common in San Francisco. Roughly, one out of every four positive cultures has come from an individual who has not had typical clinical whooping cough. The clinical diagnoses have been simple upper respiratory infection, or subacute tracheitis or bronchitis. Coughs lasting less than one week in presumably entirely susceptible children have on occasion been pertussis. Furthermore, six second attacks of pertussis have been observed. In five of these the first attack was unmistakable clinical whooping cough, not proved bacteriologically however. The second attacks were atypical but all proved bacteriologically. In the sixth instance, both first and second attacks were proved by cough plate. Similar mild second attacks are common in parents. Lastly, atypical pertussis is relatively common in children who have received phase I *H. pertussis* vaccine. All these individuals with atypical attacks are a greater public health menace than individuals with typical whooping cough. Their activities are not restricted. The procedure of isolation has, in part, failed as a public health measure because of them. The organisms they dissemi-

nate are just as virulent as those from typical cases. We have time and again noted typical cases resulting from contact with atypical cases. There are, however, a few rather interesting exceptions to this statement. These exceptions are cases of atypical cough (shall I say sometimes "suggestoid" of whooping cough), due to infection with *B. parapertussis.*

*B. parapertussis* was first described by Eldering and Kendrick.[3] Bradford and Slavin[4] about the same time reported isolating "an organism resembling *H. pertussis*" eight times in the course of 160 positive plates. Careful bacteriologic studies identified it as *B. parapertussis.* In the course of isolating 287 strains of *H. pertussis* at Stanford since 1936, my assistants have isolated this organism ten times.[5] It has been my experience that the symptoms produced by *B. parapertussis* are usually not those of clinical whooping cough. Table III summarizes our findings.

We have observed attacks of parapertussis both previous to and subsequent to attacks of pertussis. They have also been observed in three children who had received *H. pertussis* vaccine. Apparently cross immunity is absent or quite limited. The diagnosis only can be made bacteriologically. Serologic tests indicate that this organism is widespread in San Francisco but rarely produces severe paroxysmal cough which may be confused with pertussis.

*Serum Prophylaxis.*—Dr. Lewis has asked me to discuss the prophylactic value of serum in exposed individuals. My personal experience with passive immunization is limited. I have reviewed the literature and applied some simple statistical tests to the reports.

The conclusion is plain: Passive immunity has been effectively produced in infants and children with both convalescent serum and serum from adults immunized with *H. pertussis* vaccine. The reports of Bradford,[6] Paterson and co-workers,[7] Kendrick,[8] Meader,[9] Schermerhorn,[10] Cohen and Lapin,[11] and McGuinness and Bradford[12] prove the prophylactic value of serum because they are based on familial exposures and include familial controls.

How effective is serum? The best prophylaxis reported under conditions of familial exposure was that of Cohen and Lapin,[10] who succeeded in protecting twenty-eight of thirty-three children (84 per cent). This was with convalescent serum. With hyperimmune serum, Kendrick reported 82 per cent protection and McGuinness and his associates in the largest series reported 80 per cent protection. Familial exposure, as you know, produces whooping cough in 90 per cent of presumed susceptibles. Hence the protection conferred by these sera was very great. Under conditions of transient exposure the protective power of such sera would be even greater. As in measles, the less intense and the shorter the exposure, the more likely will serum protect.

Which preparation should be used, convalescent serum or the serum of vaccinated adults? The answer is whichever is available. Comparative studies as yet show no statistical difference in potency when potent batches of the two are used. This raises the problem of tests for potency. There is as yet no standard method of assaying a serum other than its protective effect against familial exposure. The demonstration of antibacterial antibody in high titer by means of agglutination or opsonocytophagic tests is almost certainly essential. The complement fixation reaction has some theoretical disadvantages,[13] but it has been widely used. Protective potency against infection in mice can be measured[14, 15, 16, 17] but is open to valid criticism.[18] The presence of antitoxin which neutralizes the pertussis toxin isolated by Evans[19] is probably not necessary. The standardization of immune sera will be attained only when a correlation can be found between a laboratory measure and protective potency against familial exposure.

What dose of serum should be given? The protective dose will depend (1) on the potency of the product, (2) the size of the patient, (3) the intensity of the

exposure, and (4) the time elapsed since the onset of the exposure. As we are all using new products, we will have to proceed by trial and error. It would seem wise for each of us to get a single source or one large lot of serum and keep it in the icebox. By using one product one can clinically calibrate its potency. There will undoubtedly be poor products and poor batches.

May I suggest that the first time you wish to protect an exposed infant of 6 months of age or younger that you use 40 c.c. of the serum you have decided to employ. This volume when divided into equal parts is about the maximum that can be injected into the thigh muscles of an infant. If it fails to protect the serum's potency, it is too low to be useful. If protection is obtained, the next time a smaller dose should be used. Thus one will learn about his serum. Try to establish the effective dose for the infant exposed in the past two or three days. Increase this dose if the child is larger, if the exposure is familial, or if the child is brought in late in the incubation period. Decrease the dose if the exposure is transient. The hope, of course, is to be able at some future date to formulate a system of dosage similar to that used in measles prophylaxis.

Under conditions of continuous familial exposure, reinjection with a second dose of serum after an interval of seven to ten days is recommended by Kendrick,[8] Schermerhorn,[10] and McGuinness.[12] The duration of the protection afforded by serum is not known. However, McGuinness[12] reported the occurrence of pertussis in a continuously exposed infant nineteen days after the injection of serum. It certainly is still the better part of valor to recommend the removal of the susceptible infant or of the whooping siblings from the home.

*Treatment.*—I have recently re-read Dr. Isaac Abt's classical paper on the "History of the Treatment of Whooping Cough."[20] May I recall it to your attention. He mentions the use in the past of cockroaches and then the entire pharmacopeia. Neither was effective. His is the view of a medical scientist, the objective, critical view which we should strive to keep. Keeping it, we must nevertheless treat our patients in the best way we know. Even though we have a feeling of inadequacy in this situation, we cannot afford to let the patients' parents catch the feeling. Although I may be entirely wrong, I have the distinct impression that the following procedures help nature heal the disease.

The child should be put to bed during the paroxysmal stage. A high humidity in his bedroom should be obtained, preferably with a modern humidifier rather than with a hot croup kettle. Five small meals should be given daily. Fluids should be given in sips of 2 ounces only every thirty minutes if possible. An expectorant, either hydriodic acid or ammonium chloride, should be forced during the day. A large dose of sedative should be given in the evening; barbital derivatives are superior to opiates because of the antiexpectorant action of the latter.[21] Codeine should be used only in the most severe cases and then at night only. The child should be allowed to cough during the day.

Pertussis pneumonia remains a very difficult problem. The sulfonamides have, of course, been used recently.[22, 23, 24] There exists a difference of opinion as to their value. No dramatic effect is to be expected in my experience. If pneumococci are isolated, or if the pneumonia has a lobar distribution rather than the more usual peribronchial distribution, then chemotherapy is very logical. Pertussis immune serum has been disappointing.[24] However, it too should be tried, preferably intravenously.

I wish to mention antigen therapy in order to condemn it. May I make the sweeping statement that *H. pertussis* vaccines, solutions, and extracts have no proved value. From personal experience, I admit the great difficulty in attempting to prove the value of any therapeutic agent in whooping cough. We should be charitable to all undertaking this task when they control their observations. On the other hand the tremendous variability in the course of this disease makes uncontrolled studies valueless.

TABLE III

SUMMARY OF CLINICAL RECORD

(GROUPED IN REGARD TO TYPE OF HISTORY)

| CASE AND DATE | AGE | SEX | PAST HISTORY | EXPOSURE TO "WHOOPING COUGH" | COUGH | | | POST-TUSSIC VOMITING | NASAL DISCHARGE | DAY COUGH PLATE POSITIVE | CLINICAL DIAGNOSIS | SUBSEQUENT HISTORY |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | TYPE | WHOOP | DURATION (DAYS) | | | | | |
| G. G. 7/38 | 14 mo. | M | -- | None known | Paroxysmal; not severe | -- | 23 | Once | Purulent | Tenth day | Upper respiratory infection | Negative |
| H. G. 3/39 | 7 yr. | M | -- | None known | Paroxysmal; not severe | -- | † Improving on twelfth day | Twice | -- | Seventh day | Mild whooping cough; WBC = 9,480, 45% lymph. | Negative |
| G. N. 6/40 | 6 yr. | M | --* | None known | Paroxysmal; severe | + | 36 | Repeatedly | -- | Tenth day | Typical whooping cough; WBC = 22,400, 70% lymph. | Negative |
| S. R. 1/37 | 6 mo. | F | -- | None known | Paroxysmal; mild | -- | 14 | -- | Mucopurulent | Second day | Upper respiratory infection | Seven months later typical moderate severe whooping cough; WBC = 35,900, 69% lymph. |
| H. S. 6/39 | 5½ mo. | F | -- | None known | Paroxysmal; mild | -- | 21 | Once | Slight mucopurulent | Sixth day | Mild whooping cough | One year later typical moderate severe pertussis cough plate + |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| N. F. 7/38 | 10 yr. | M | Whooping cough at 3 years; WBC = 37,600, 67% lymph.; treated with vaccine | Familial exposure to sister G. F. (see below) for 9 days ā onset | Mild; paroxysmal; night only | -- | 7 | -- | -- | Third day | Tracheitis | Negative |
| G. F. 6/38 | 7 yr. | F | Whooping cough at 3 months; brother had lymphocytosis (see above); treatment by vaccine | None known | Mild; paroxysmal; night only | -- | 14 | -- | -- | Seventh day | Tracheitis | Negative |
| W. W. 6/39 | 2½ yr. | M | *H. pertussis* vaccine; 80 billion; twenty months previously | Indoors for 8 hours; 8 days ā onset | Nonparoxysmal | -- | 5 | -- | Profuse mucopurulent | Fourth day | Upper respiratory infection | Negative |
| P. S. 6/39 | 5½ yr. | F | *H. pertussis* vaccine; 80 billion; four months previously | Familial exposure to sister H. S. (see above) for 6 days ā onset | Nonparoxysmal | -- | 17 | -- | -- | Tenth day | Tracheitis | One year later familial exposure to pertussis in sister H. S. (see above); escaped entirely |
| D. R. 7/40 | 23 mo. | M | *H. pertussis* vaccine; twenty billion cells; given only seventeen months previously | None known | Paroxysmal; severe | + | 27 | Several times | Mucopurulent | Fourth day | Whooping cough; WBC = 10,600, 36% lymph. | Negative |

*One cubic centimeter of *H. pertussis* vaccine (20 billion cells) was given elsewhere on the sixth day of cough.

There are at present, as always, some therapeutic rays of hope. The brightest hope certainly is immune serum, either the convalescent or the hyperimmune variety. The reports of Katsampes, McGuinness and Bradford,[25] of McGuinness, Bradford, and Armstrong,[12] of Cohen, Weichsel, and Lapin,[26] and of Williams[27] are encouraging. Certainly no serum should be tried therapeutically unless it is highly effective prophylactically. The vacuum dried "pertussis immune" serum produced by the Philadelphia Serum Exchange is of Undoubted prophylactic value, as may be seen in the charts in the exhibit. Dr. McGuinness, Director of the Serum Exchange, has kindly furnished me with a summary of 315 cases of pertussis treated with serum. At least 60 c.c. of serum were given in divided doses of 20 c.c. at two-to-three-day intervals. An "excellent" therapeutic effect was obtained in 37 per cent of the cases and a "good" result in an additional 31 per cent. In me this information raises high hopes, for my own experience with other sera has not been so happy.

Another ray of hope has just appeared on the horizon, or rather reappeared as Dr. Abt recalls that it was tried years ago. I refer to the use of inhalations of carbon dioxide suggested by Dr. Poncher of Chicago in a footnote to a report on expectorants by Holinger, Basch, and Poncher.[21] Bronchoscopic observations revealed that carbon dioxide was a highly effective expectorant in bronchiectasis, whereas oxygen exerted an antiexpectorant action. Believing that expectorants are rational in whooping cough, I hope that a careful study of carbon dioxide will be made in this disease.

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## DISCUSSION

DR. J. B. WALL, Washington, D. C.—How extensively is the cough plate used in diagnosis?

DR. KENDRICK.—The use is limited to large health departments. Unless the media are kept constantly made up, it is difficult to obtain good plates when they are wanted. The cough plate must be taken properly by a physician and examined by a competent bacteriologist.

DR. P. J. McGUIRE, HOMESTEAD, PA.—The cough plate was tried extensively at the Children's Hospital in Pittsburgh but was given up. Is it practical for the ordinary community?

DR. KENDRICK.—It takes about six months for an interested and experienced person to learn to obtain good plates. A good medium is necessary, which should be properly standardized. A good source of blood should be available. I advise the use of sheep blood for preparation of the media.

DR. MILLER.—There is a lack of technicians with training in the bacteriology of *H. pertussis*. Most bacteriology courses need more emphasis on *H. pertussis*.

DR. A. C. McGUINNESS, PHILADELPHIA.—Some donors selected for the preparation of hyperimmune serum may receive 50 to 100 c.c. of vaccine without demonstrating any titer in the blood. These are individuals who never seem to show an immune response. We have observed the following results in the use of hyperimmune human serum:

1. *Prophylaxis.*—In a group of sibling contacts without isolation, 67 per cent of eighty children did not develop pertussis after receiving two doses of 20 c.c. each five days apart. This passive immunity only lasts about two weeks.

2. *Treatment With Hyperimmune Serum.*—The data will probably take years to evaluate properly. In a group of 123 infants treated, 3 died. None of the three who died received three injections of 20 c.c. each at forty-eight-hour intervals, which we consider the proper therapeutic dose. Sixty-eight per cent of the treated patients showed good results in that one week after the first injection of serum the paroxysms virtually had stopped. The donor should have an agglutination titer of at least 1:1280 with the vaccine used to give blood to be used in therapy. Our present need is to find the best way to immunize the donors and what titer is important to use in selecting the donors.

DR. K. S. LANDAUER, GENEVA, N. Y.—I have treated with hyperimmune serum a group of six infants under 6 months of age who had pertussis bronchopneumonia and observed excellent results.

DR. H. C. CLARK, NEW ROCHELLE, N. Y.—What is the dose of convalescent serum?

DR. MILLER.—The dose is not certain. The hyperimmune serum of the Philadelphia Serum Exchange is administered in a dose of 10 c.c. in each thigh. Commercial houses are now starting to produce these sera.

DR. C. H. WEBB, SHREVEPORT, LA.—Is serum given intravenously?

DR. MILLER.—No.

DR. LANDAUER.—The New York State vaccine may not be a good antigen. The sediment clumps in the vial.

DR. KENDRICK.—The dispersion of the vaccine is not important. The strains used in production of the vaccine are the most important feature and should be hemolytic, agglutinable, lethal to mice, and produce skin reactions in rabbits.

DR. CLARK.—What is the present New York State vaccine?

DR. MILLER.—I think the vaccine is now produced with freshly isolated strains.

DR. CLARK.—Is the opsonocytophagic test at the maximum two months after the immunization has been completed?

DR. KENDRICK.—Yes. This does not necessarily mean that clinical protection is greatest at this time. There are some children who develop no immunity. This is brought out by second attacks in the same child.

DR. F. T. CAVANAUGH, TROY, N. Y.—Is vaccine better which is prepared on media containing human blood?

DR. KENDRICK.—I see no advantages in using human blood.

DR. M. B. LOW, GREENFIELD, MASS.—How would you immunize an infant 6 months of age?

DR. KENDRICK.—Seven cubic centimeters of a 10 billion suspension of *H. pertussis* at the following intervals: start, 1 c.c.; one week later, 1.5 c.c.; one week later, 1.5 c.c.; three weeks later, 1.5 c.c. each arm. We may find it better to scatter the dosage over a longer period of time.

DR. P. S. BRADSHAW, MUSKEGON, MICH.—Do you observe a sore arm after the second injection?

DR. KENDRICK.—I have not heard of this before. There are few reports of slight general reactions. Most patients will have a slight temperature rise if the temperature is taken.

DR. R. C. BATES, PROVIDENCE, R. I.—What is your opinion of injections in the leg?

DR. KENDRICK.—We have observed more reactions after injections in the leg. In a group of forty infants, more discomfort was reported after leg injections than in a similar group with injections in the arms.

DR. M. S. HIRSHBERG, HARTFORD, CONN.—What is your opinion of giving "booster" doses?

DR. KENDRICK.—It is reasonable to give a secondary stimulus at some time later and especially at the time of entrance to school. However, there is no exact answer based on experience.

DR. MILLER.—What dose should be used as a "booster" dose?

DR. KENDRICK.—A small dose is sufficient. Typhoid revaccination demonstrates this point.

DR. G. SANCHEZ, GUATEMALA CITY, GUATEMALA.—How often do you revaccinate?

DR. KENDRICK.—One-half of a cubic centimeter every year is sufficient, or even $\frac{1}{10}$ c.c. intracutaneously. Pertussis immunization is good for at least two years.

DR. W. P. McDOWELL, NORFOLK, VA.—At what age do you start immunization?

DR. MILLER.—I start at 5 months. I am going to try it at an earlier age.

DR. KENDRICK.—It is best given at 6 months of age, because results seem better and it is also safer.

DR. MILLER.—We have no evidence that we cannot immunize a 2-month-old infant. There is no evidence that vaccine does any good after exposure.

DR. BEN BENJAMIN, MONTREAL.—Why is there a difference between Sauer's vaccine and Kendrick's vaccine?

DR. KENDRICK.—One should not expect a difference in antigenicity.

DR. J. W. CANADAY, GLENS FALLS, N. Y.—I get reactions using double strength Sauer vaccine.

DR. E. S. WEGNER, LINCOLN, NEB.—We get more reactions when the vaccine is cold. We also give the vaccine in the afternoon, accompanied by a dose of phenobarbital to prevent reactions.

DR. MARGARET M. NICHOLSON, WASHINGTON, D. C.—Do you get abscesses of the arm with alum-precipitated material?

DR. KENDRICK.—We have had two cases. We think these abscesses were caused by superficial injections.

DR. MILLER.—There are more reactions in older children with alum injections than in younger children.

DR. JOHN LANGDON, PROVIDENCE, R. I.—How close to giving other immunizations can we give pertussis vaccine?

DR. KENDRICK.—As close as necessary. We have good results in the use of combined pertussis vaccine and diphtheria toxoid.

DR. MILLER.—I believe concurrent vaccination is possible. We have had good results with combined tetanus toxoid, diphtheria toxoid, and pertussis vaccine.

DR. G. C. GLASS, HARTFORD, CONN.—Are there any anaphylactic reactions after 3 months with pertussis vaccine?

DR. MILLER.—Not that I know of.

DR. BENJAMIN, MONTREAL.—Ether by mouth seems to work better than ether by rectum in the control of the paroxysms.

DR. SANCHEZ.—We give ether inhalations in oxygen twice daily and get good results.

DR. CLARK.—Is a binder still used?

DR. MILLER.—I do not know.

DR. LEWISON.—Would you keep windows open or closed on the basis of carbon dioxide treatment?

DR. MILLER.—I would advise keeping windows open. The administration of carbon dioxide is experimental, and only a whiff or two are given to the patient.

DR. H. S. HEERSMA, KALAMAZOO, MICH.—It is difficult to evaluate therapeutic results. You get best results with what you use. I get good results with atropine and codeine. I get poor results with expectorants, as the mucus gets thick and congeals in the trachea. I get better results with medical measures than with serum.

# ELEVENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

BOSTON, MASSACHUSETTS—OCTOBER 11, 1941

## Panel Discussion on Clinical Aspects of Growth and Development

Chairman: Arnold Gesell, Ph.D., Sc.D., M.D., New Haven, Conn.
Associates: L. Emmett Holt, Jr., M.D., Baltimore, Md.
Catherine S. Amatruda, M.D., New Haven, Conn.
Winthrop M. Phelps, M.D., Baltimore, Md.
C. Anderson Aldrich, M.D., Chicago, Ill.

CHAIRMAN GESELL.—Last spring the members of the American Academy of Pediatrics were circularized with a kind of Gallup poll and given an opportunity to express their preference as to the panel subjects. It is interesting to note here that the subject of Growth and Development stood far in the lead. (I have heard rumors about someone on the Atlantic seaboard who said he did not believe in growth and development, but I think it was not a pediatrician.)

A vote so decisive can mean only one thing; namely, that development as well as disease is now a recognized concern of clinical pediatrics.

This is a natural and inevitable evolution. It was in the cards. As soon as the pediatrician took over the nutrition of healthy as well as sick babies, he accepted wider tasks, at least by implication. He became interested in positive medicine and in the protection of maximum physical growth. But this protection took him into a whole host of problems of child care, of complicating mental factors in the parents, of individual differences in the infants. These differences proved to be not purely physical; they had a psychic aspect. He found that the clinical manifestations of physical and mental welfare were interdependent, that the boundary between normal and abnormal was neither sharp nor fixed but shadowy, shifting, and always subject to developmental maturity.

The medical sciences likewise have been breaking down old-time distinctions between normal and abnormal, between structure and function, between mind and body. Pediatrics remains, as Osler so aptly put it, the specialty of general medicine. But general medicine has become psychosomatic medicine. It hyphenates mind and body, which means that the clinician who attempts to appraise the total child must take into account all types of symptoms, including those which go by the name of behavior. The behavior patterns of infant and child are the most comprehensive index of the integrity and maturity of his nervous system. General medicine, it might be said, ceases to be general medicine when it overlooks or ignores behavior symptomatology. It is impossible to diagnose the developmental status of an infant or child without applying psychosomatic norms, including norms of behavior maturity. A man may be as old as his arteries; an infant is as old as his behavior.

Successful diagnosis, prognosis, guidance, and supervision all demand a shrewd appraisal of behavior equipment, behavior potentialities. This is true not only of the staple behavior problems, anorexia, thumb-sucking, enuresis, tantrums, etc. It is even more true of those important and more permanent conditions which are primarily developmental. These conditions come to the attention of the pediatrician (or family physician) first of all. He has the ground-floor opportunity to make the initial diagnosis and to set parents right. The conditions are legion.

They include amentia (mental deficiency), cerebral injuries acquired before, during, or after birth, convulsive disorders and endocrine disorders, sensory handicaps, partial blindness and deafness, environmental retardation from institutionalization and hospitalization, and numerous neurologic deviations and deficits. None of these conditions can be adequately diagnosed or interpreted without an appraisal of behavior characteristics.

And the well babies of preventive pediatrics likewise need the protection of developmental examinations, directed toward a periodic appraisal of behavior assets and behavior liabilities. We are well aware that there is a vast, steadily rising demand for professional parent guidance and a closer clinical oversight of infants and preschool children. The future holds a broader type of periodic medical examination if pediatrics meets the challenge.

In a recent symposium on advances in psychology* it was suggested that the preoccupation of medicine should "continue to be with the abnormal and pathologic manifestations of life; whereas psychology naturally would and should be occupied with the normal or typical personality." This formula would set up a professional psychologic service for infants and young children. Such an envisagement is, in my opinion, contrary to both the trends of modern science and clinical medicine. The movement of the medical sciences is toward a unification, toward a single, monistic outlook in all symptomatology, and therefore to an intensification of general medicine, which is pediatrics, and which in turn means an integrated psychosomatic medicine.

As we open this panel discussion it is interesting to recall that the elder Doctor Holt in his pioneer work and in his two famous books on *The Care and Feeding of Children* and *The Diseases of Infancy and Childhood* showed a keen perception of the importance of the mental and developmental aspects of child hygiene. I can see him giving an approving nod to the type of program which the Academy has arranged for this Boston meeting. We are preserving the developmental continuity of American Pediatrics when we call on Dr. L. Emmett Holt, Jr., who in his own right will discuss relationships of nutrition and development, with special reference to dietary factors in physical growth.

## Dietary Factors in Physical Growth

**L. Emmett Holt, Jr., Baltimore**

In discussing the relation between diet and growth, I want first of all to raise the question as to whether maximal growth and optimal growth are identical. It is often assumed that they are. "The bigger the better" has been called our American slogan. I should like to point out that this is still an open question. In certain rat experiments stimulation of growth has resulted in a decrease in longevity. It is clear that an abundance of good food tends to increase the size of the species, but we do not know that there is any corresponding increase in gray matter. The carboniferous age produced the dinosaur, a marvelous animal but not blessed with brains. In our own species there is evidence that with our newer knowledge of nutrition the human animal is getting bigger. Harvard sons are taller than their fathers, but there is no clear evidence that the Harvard sons are more acute or more agile than their fathers. It may be that in time we shall find that the most successful individual in life is the small, wiry individual rather than the Goliath. I shall not dwell on the obvious disadvantages of size, the discomforts of Pullman berths, of low ceilings, and of blankets designed for the average man rather than for the favored few who have come under the care of the nutritionally enlightened pediatrician. But with these remarks I shall pass on to the factors concerned in physical growth, leaving it for the future to decide whether maximal and optimal growth are identical.

*Proceedings of the American Philosophical Society, Philadelphia, 1941: volume 84.

The growth factors now accepted as essential for the human species are shown in Table I.

TABLE I

ESSENTIAL FOODS FOR GROWTH

I. Calories
II. Essential Amino Acids:
    Tryptophane
    Phenyl alanine
    Histidine
    Lysine
    Leucine
    Isoleucine
    Methionine
    Valine
    Threonine
III. Minerals of Extracellular and Intracellular Fluids:
    Na, K, Ca, Mg
    Cl, P, S
IV. Trace Elements:
    Fe, Cu, Mn, Zn, I, F,
    ? Co
V. Accessory Food Factors
    Fat soluble vitamins:
        A, D, K, ? E
    Ascorbic acid B complex:
        Thiamin
        Riboflavin
        Nicotinic acid
        ? Pyridoxine
        ? Pantothenic acid
        ? Choline
        ? Para amino benzoic acid
        ? Biotin
    ? Essential fatty acids
VI. Water

It is fortunate for our peace of mind that we do not have to calculate these thirty or more factors in feeding our patients. Too little is known about the content of many of these factors in our common foods, and the list of dietary essentials is based largely on rat experiments rather than on observations in man. It has recently become clear that even closely related species differ in their requirements of essential amino acids, minerals, and accessory food factors. It is necessary to work out the food requirements of man by experiments on the human subject before we can really talk about scientific feeding, and it will be many years before this knowledge is available.

The human requirements for essential amino acids are completely unknown. The only observation of which I am aware is a single unpublished experiment performed by Dr. Warren M. Cox, Jr., of Evansville, Ind., demonstrating the need for tryptophane. Last summer Dr. Albanese and a group of workers in Baltimore tackled this problem; they fed human volunteers on mixtures of pure amino acids as their only source of nutrition and determined their nitrogen balance. I shall present some of the results because they have led to at least one conclusion different from that based on rat experiments (Figs. 1-3).

You will note that tryptophane and arginine deficiency leads to a negative nitrogen balance and are obviously dietary essentials for man. Arginine deficiency, however, does not produce this result, from which one might conclude that, like the rat, man does not require arginine. We found, however, that the human male, although he can maintain his nitrogen balance for a time without arginine, does so at the expense of his spermatogenic tissue, a tissue rich in this amino acid. The arginine deficiency caused the numbers of spermatozoa produced by these subjects

to fall off sharply and motile forms practically disappeared. They reappeared when an arginine supplement was added. These observations were made by Dr. Shettles. It is thus clear that arginine must be included in a list of amino acids essential for human maintenance, and I think we can assume that it is likewise essential for normal human growth.

I mention these experiments only to emphasize our ignorance of human dietary requirements and to point out the need for further work along this line. It is of particular importance that we learn all we can about the amino acid requirements of man. When animal proteins are abundant we do not have to worry, because such proteins have high biologic values. There is, however, a great shortage of animal proteins in Europe, and with the increased demands made on this country for food there are indications of an impending shortage here. It behooves us then to learn to utilize the incomplete vegetable proteins to the best possible advantage.

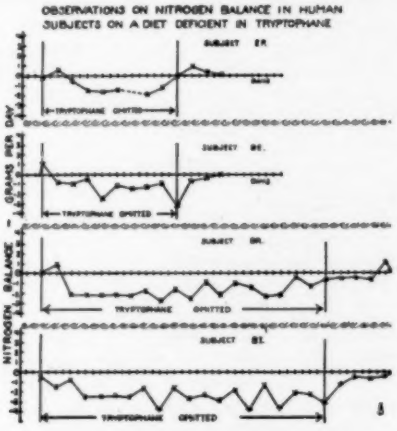

OBSERVATIONS ON NITROGEN BALANCE IN HUMAN
SUBJECTS ON A DIET DEFICIENT IN TRYPTOPHANE
NITROGEN BALANCE - GRAMS PER DAY
TRYPTOPHANE OMITTED

Fig. 1.

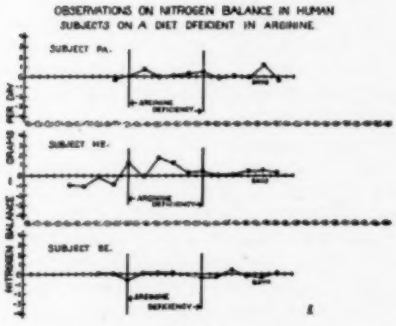

OBSERVATIONS ON NITROGEN BALANCE IN HUMAN
SUBJECTS ON A DIET DFEICIENT IN ARGININE
NITROGEN BALANCE - GRAMS PER DAY
ARGININE DEFICIENT

Fig. 2.

I shall try to come down to earth now and devote the remaining minutes of my time to drawing a few practical conclusions from recent studies on nutrition.

We have learned that proper nutrition begins in fetal life. It is clear that better bones and teeth are secured by the administration of adequate vitamin D and calcium during pregnancy, and that an adequate iron intake during pregnancy often will prevent the development of anemia in the child. Even more arresting

is the possibility of preventing malformations in the young by the maternal diet, a fact which Warkany* has so ably demonstrated in rats.

We have lost much of our religious awe of breast milk. It is known in many respects to reflect the maternal diet in its composition rather than to be an ideal nutriment designed by the Creator. We now know that its fat does not represent the ideal but tends to reflect the fat recently eaten by the mother, that its protein content may be inadequate for some premature infants, that it may supply insufficient iron for hemoglobin formation and, most important of all, that it is often deficient in vitamins. These shortcomings are seen particularly in the underprivileged economic groups in which the maternal diet is often inadequate in some respects. It is our task to protect the nursing infant from these shortcomings. This can often be done by improving the maternal diet, but it is safer to insure the child's intake by giving supplements. I think we are on sound ground when we give supplements early. Supplements of C and D are of particular importance; supplements of iron and of the B factors may be introduced in the form of natural solid foods or, quite as satisfactorily, by means of cereals which are reinforced in these respects.

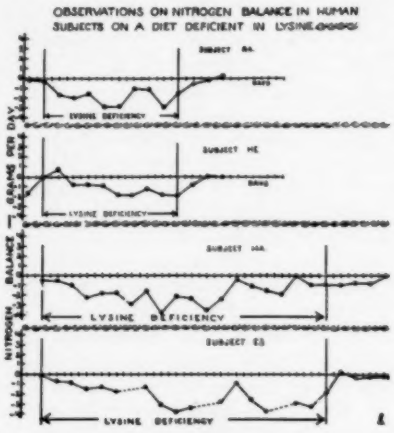



Fig. 3.

I think the recent tendency to give solid food early to the artificially fed infant is also a sound one, since its net result is to provide iron and vitamin supplements and to provide these supplements in a balanced form.

I want to say a few words about the food requirements of the sick infant. They may differ greatly from those of the healthy infant. Food ingested may be incompletely absorbed in disease, it may be poorly utilized after absorption, and there may be a greater requirement of one or another foodstuff or factor caused by the increased metabolism associated with fever. I cannot go into this subject extensively but will call attention to a single example only, the increased requirement for thiamin in diarrheal states. We pediatricians owe Dr. Sydenstricker† a debt of gratitude for calling this to our attention. He was struck by the frequency with which local edema developed in diarrheal patients who were given only venoclysis with glucose and saline, and it occurred to him that the usual explanation of such edema on a hydrostatic basis was inadequate. He made the observation that such edemas often could be prevented or cured by thiamin and

*Warkany, J., and Nelson, R. C.: Skeletal abnormalities in the offspring of rats reared on deficient diets, Anat. Rec. 79: 83, 1941.

†Sydenstricker, V. P.: Ann. Int. Med. 14: 1507, 1941.

pointed out that the use of glucose as the sole food under these circumstances tended to further deplete an already inadequate supply of thiamin. I wish to offer you some further evidence in support of Dr. Sydenstricker's thesis that thiamin deficiency is a frequent accompaniment of diarrhea.

TABLE II

THIAMIN EXCRETION TESTS IN INFANTS WITH DIARRHEA

| PATIENT | AGE (MONTHS) | 4-HOUR EXCRETION IN URINE (μG) AFTER 1 MG. BY VEIN | STOOL CULTURE | COMMENTS |
|---|---|---|---|---|
| M. H. | 10 | 279 | | Moderate severity (brief duration) |
| N. J. | 10 | 220 | | Mild case |
| J. W. | 14 | 214 | Dysentery | Moderately severe |
| G. Y. | 4 | 187 | | Moderately severe |
| C. H. | 9 | 170 | | Moderately severe |
| N. S. | 10 | 138 | Dysentery | Moderately severe |
| C. A. | 9 | 130 | | Severe case |
| F. Z. | 13 | 112 | Dysentery | Severe case |
| W. T. | 7 | 68 | | Moderately severe |
| R. B. | 5 | 50 | Dysentery | Severe case |
| Normal range | 6-24 | 260-338 (Av. = 302) | | |

This past summer we have applied the thiamin excretion test in a number of patients with diarrhea and you will note from Table II that nine out of ten consecutive patients showed retention of thiamin beyond the normal averages. The more severe degrees of thiamin depletion were seen in the more severe cases, most of which received infusions of glucose. We were not able to establish the presence of neuritis in any of these subjects, but Sydenstricker has observed it developing under such circumstances. The moral is that we should give thiamin, preferably with other B factors, under these circumstances.

I want to make a few concluding remarks about the prevention of deficiency disease which is, after all, a problem identical with that of securing maximal growth. Despite the enormous exploitation of vitamins and an unparalleled national expenditure for these products, we still have deficiencies with us. For example, Dr. Park has recently found evidence of active scurvy in more than 12 per cent of the autopsies on Baltimore infants of suitable age, and this in spite of the propaganda carried on by physicians, infant feeding stations, and the publicity of citrus fruit growers and manufacturers of ascorbic acid. It seems as if the problem cannot be satisfactorily solved by vitamin supplements. A more foolproof method must be adopted; namely, complete fortification of the milk supply used for infant feeding with all essential mineral and accessory factors. I believe that we shall see this in a relatively short time. There are technical difficulties, such as the incorporation of vitamin C in stable form, but there are indications that these difficulties can be overcome. With such a food and with suitable legislation to control its standards, deficiency disease in the young subject should receive its death blow and a major cause of impaired growth will have been removed.

CHAIRMAN GESELL.—You have made it very clear that the dietary factors have considerable significance from the standpoint of developmental differentiation as well as from the standpoint of nutrition.

You spoke of the species differences in breast milk and, of course, there are species differences in breast milk. Do you think that these biochemical differences hold equally for individual patients and are of the same character?

DR. HOLT.—There are instances of siblings and of twins living in the same household in which one infant developed rickets and the other failed to do so. Such observations suggest that there are differences in the requirements of individual subjects for these food factors.

DR. ALDRICH.—Dr. Holt spoke of preventing nutritional disease by feeding babies some milk which contained known vitamins. I do not understand how we are going to supply the vitamins that will be discovered tomorrow or in the next few months.

DR. HOLT.—As new vitamins are discovered we will include them in our diets.

DR. ALDRICH.—It seems to me we have to consider something more than the drugstore method of supplying those vitamins. I think we should get back to what might be called nature fakir diets, where we use foods unchanged by modern techniques. Then we might get a diet which contained those vitamins that we do not know about.

DR. HOLT.—I do not like the term "nature fakir" but I think Dr. Aldrich has a sound idea.

CHAIRMAN GESELL.—I am now going to call on the second speaker who will make use of the cinema to demonstrate the clinical implications of a developmental approach to the neurology of the infant.

Dr. Catherine S. Amatruda is in charge of an active infant outpatient service in connection with the Clinic of Child Development of the Yale School of Medicine. The Clinic has made it a practice to document the most instructive cases with motion picture records. Dr. Amatruda will show selections from these records which illustrate not only the clinical conditions, but also the methods of developmental examination.

## Developmental Neurology

**Catherine S. Amatruda, M.D., New Haven**

*Introductory Comment.*—It is generally stated that the examination of the neuromotor system of the infant is difficult and on the whole unsatisfactory. Perhaps this statement has been a little too readily accepted. In the Clinic of Child Development at Yale we have developed a systematic method of examination which discloses both the maturity of the developing nervous system and also its integrity. With a knowledge of normal behavior patterns and a knowledge of the development of these patterns and their coordination with each other, we can recognize the presence or absence of these patterns, whether they are normal or deformed and abnormal, and we can interpret the significance of the patterns we see. The developmental examination is a practical method for appraising the competence of the neuromotor system.

The film shows first a few selected normal neuromotor patterns at salient ages, their progress and development; and second, a series of selected clinical cases with varying degrees of neurologic impairment. These are not presented as case reports but to demonstrate samples of abnormal behavior, abnormal neuromotor signs.

Although gross defects are represented in the film, the emphasis is on some manifestations of minimal cerebral injury, a condition which can produce very abnormal behavior patterns in infancy and which often leads to an erroneous diagnosis of mental defect.

***At this point a film entitled "Developmental Neurology" was demonstrated with comment as follows.***

NORMAL NEUROMOTOR PATTERNS

*4 Weeks.*—A normal infant in a simple postural test; he is pulled upright and then supported in the sitting position. At this age the head lags during the pull, and in the sitting position the neck and back are passively flexed, producing this typical posture.

*16 Weeks.*—(a) In the same postural test three months later the normal infant shows only a slight head lag during the pull. He holds the head fairly erect and the back is bowed only in the lumbar region, though the trunk still needs support. (b) Another simple neuromotor test: a cube is placed in easy reach on the table before the infant. At this age the infant looks at the cube and activates his arms but he is unable to bring them very close to the cube. He looks back and forth from his hand to the cube.

*28 Weeks.*—(a) This infant sits leaning forward, propped on his hands; the legs are flexed and used as outriggers for lateral balance. Head control is well established. (b) Presented with a cube, he makes a very direct prehensory approach upon it, picks it up with a whole hand grasp, brings it to his mouth and transfers it from hand to hand. His prehension and manipulation are still somewhat crude and inaccurate.

*40 Weeks.*—(a) By 40 weeks the infant sits with good control, the back straight, the legs slightly flexed and abducted. He can lean forward and re-erect himself and his hands are free for grasp and manipulation. He does not fall, but can deliberately go from sitting to prone. (b) In a prehensory situation, two objects can be grasped, one in each hand. The grasp is digital, the use of the index finger is prominent. The two objects are brought into simple combination.

*52 Weeks.*—(a) Sitting having been mastered at the preceding age, only the cube situation is shown. Instead of bringing two cubes into a simple side-by-side relation, this infant tries to release one upon the other. His failure to produce a stable tower of two cubes is due to his normal awkwardness in releasing an object.

ABNORMAL NEUROMOTOR PATTERNS

*Spastic Paraplegia* (Age, 32, weeks).—(a) This infant shows a strong tendency to asymmetrical (tonic neck reflex) posturing of the arms which reverses itself repeatedly and automatically. The pattern is abnormal at this age and abnormal in its rhythmic alternating automaticity. The legs are rigidly extended, a leg posture which does not comport with the asymmetry of the arms. The toes show a tonic Babinski reflex.

*Minimal Cerebral Injury* (Age, 36 Weeks).—(a) This child shows extremely poor head control; he cannot sit alone and his trunk slumps even in the supporting chair. He shows a wandering type of attention, though the facies is alert. He does not use his hands in a prehensory situation and does not even show reflex grasping when an object is pressed into his hand. The fingers tend to be extended and adducted, and the hands show slight athetotic movements. (b) In supine also he does not use his hands to approach objects but he does approach an object with his head, a feat that would seem to be more difficult. This is a displacement of the reaching reaction; a substitute pattern in the face of motor disability, due to a minimal cerebral injury. (c) His abnormal sitting patterns are now demonstrated. Head and back are bowed as in the very young infant, but the legs are extended and adducted, offering no lateral balance, the arms withdrawn, offering no forward balance.

*Mild Athetosis* (Age, 40 Weeks).—(a) In a prehensory situation this infant keeps his hands fisted and he is unable to lift them against gravity. In contrast to the preceding case, however, he approaches the test object, sliding his hand along the table, and slowly and laboriously grasps the toy. In manipulation the two arms do not operate freely and independently; the upper arm is adducted

close to the chest and when he rotates one arm, the other rotates synchronously. (b) He is very hypotonic in the sitting situation and is unable to erect himself against the forces of gravity. The legs are extended and adducted, the toes in tonic plantar flexion. This same boy (Boy A) will be shown at later ages. He finally manifested an athetosis of moderate severity.

*Minimal Cerebral Injury* (Age, 44 Weeks).—(a) This girl also does not sit unsupported. Instead of a robust approach and manipulation, she merely touches objects and seems to be content with this very incomplete and imperfect manipulatory pattern. Her finger posturing is unusual. She also fails to grasp objects reflexly; indeed it appears as though she were refusing to accept objects; actually when she finally grasped a cube, she was unable to release it voluntarily, her grasp was so spastic. (b) In the prone position she rolls to the side and props up on one elbow, a position which elevates her head and frees one hand and may be considered a substitute sitting pattern. This also is a minimal cerebral injury with deformation of normal neuromotor patterning.

*Minimal Cerebral Injury* (Age, 48 Weeks).—(a) This boy sits only with support, the head bent forward. The haziness of his facial expression and attention bespeaks a visual defect. The posture of arms and hands is peculiarly bow-legged. Hand and finger patterns are very atypical. He, too, does not grasp but satisfies himself with touching, tipping, etc. Even when the hand is perfectly poised for grasp and the approach accurate, he still fails to grasp. He also fails to grasp an object pressed into his palm; indeed his exploitive pattern interferes with grasp. He, too, rotates both arms to rotate one.

*Mild Athetosis* (Age, 52 Weeks).—(a) This is Boy A again, whose hypotonic sitting at 40 weeks was shown. He shows considerable improvement and is now able to sit unsupported. The patterning is, however, distinctly abnormal. The legs are still extended and adducted, the toes hyperextended; he leans far forward and props on at least one hand. Balance is precarious but he can lift one arm without falling over; he is beginning to integrate and coordinate his sitting even though very imperfectly.

*Severe Athetosis* (Age, 56 Weeks).—(a) This infant was born prematurely, suffered a severe jaundice in the neonatal period, and later was smothered in his crib and was resuscitated. He is grossly retarded and shows typical athetotic patterns: accessory arm movements, hand and finger posturing, and twiddling. His sitting stance is similar to that of the less severely damaged children previously shown.

*Minimal Cerebral Injury* (Age, 56 Weeks).—This is another child of the same age. He sits alone, is smiling, alert, and interested. He is, however, a very incompetent exploiter. He holds his arms closely adducted to his chest; he touches objects without grasping them, and he shows mild athetotic hand movements and a few individual patterns such as scratching with his thumbs. If the table is removed and a toy placed on the platform he spontaneously displays his substitute exploitive patterns, kicking a ball accurately without losing his sitting balance, while his hands hover helplessly and uselessly out of prehensory range. This is his "natural" method and he has developed it remarkably well.

*Cerebellar Aplasia* (Age, 2 Years).—This girl is an ament in spite of her alert, attractive appearance. She has a cerebellar aplasia and she is included to show the very marked tremor which interferes with her performance. She tries to control this tremor by bracing against the table; in spite of her obvious disability she grasps and manipulates more adeptly than many of the less handicapped children you have seen. She tends to hide her tremor, not too unsuccessfully, until she has to reach out into space. Many tremors and ataxias are disclosed only in this way. Her tremor and hypotonia become very marked in the standing position.

*Mild Athetosis* (Age, 2½ Years).—This is Boy A again, and he now shows an athetosis of moderate severity. Intellectually he is quite normal. The athetosis

shows in his tower building, where his placement is inaccurate; it also shows in the posturing of his free hand when he is controlling the movements in the hand he is using. It shows in his walking; he walks backward and sideward before he can walk forward and his involuntary movements tend to throw him off his course. When asked to kick a ball, he first offers a substitute performance, throwing. He finally walks into it, a very immature pattern not better than an 18-month-old child can do. In this boy it is another symptom of his disability, as all these abnormal patterns are symptomatic of disability and neuromotor impairment.

CHAIRMAN GESELL.—We will not pause for discussion at this point because the next paper continues with the same subject, namely the developmental aspects of neurologic defects.

To sum up, it would seem as though Dr. Amatruda has demonstrated that even such simple objects as a pellet and a cube may be used productively for clinical purposes in exploring the developmental maturity and in defining the integrity of the nervous system. The central nervous system is after all the most important organ system of the child, and most of the clinical procedures of adult neurology are not applicable to the infant. We need to approach this nervous system by other techniques, including the developmental examination of infant behavior patterns.

Dr. Phelps is going to speak out of a vast experience with children who have suffered from neuro-orthopedic handicaps of different kinds. His patients have benefited by his sympathetic methods as well as by his developmental insight.

## Maturity Factors in Neuro-Orthopedic Handicaps

Winthrop M. Phelps, M.D., Baltimore

Neuro-orthopedic handicaps can be classified in several ways. First, as regards the location of the lesion, they may have origin in the brain, spinal cord, or in the peripheral nervous system. More important, from the maturity standpoint, is the time at which the lesion occurred. A lesion present from the time of birth or acquired within the first two weeks of life will result in a very different final clinical picture from that seen in an identical lesion acquired later. This is because certain normal developmental characteristics of the motor system have been primarily prevented in the first case but had been previously learned and then interfered with in the second. The study of the normal maturity characteristics can be greatly aided by observation of the reactions when normal motor development is blocked.

There are four clearly defined motor developmental periods which can be studied. The first of these is from birth to 18 months of age. During this period the infant establishes at least four basic and fundamental mechanisms. *Balance,* which includes consciousness of position of the body as a whole, as well as the extremities individually, is developed during this period from simple rolling to unsupported standing. *Reciprocation* of the legs begins with the exercise of kicking the sheet off the legs and progresses through crawling to actual walking and running. The *reach and grasp* function in the arms, beginning with examination of the hands and seizing of simple objects, develops into feeding, grasping objects for support, and reaching for toys and books. *Speech,* beginning early with the simple vocalization of crying, progresses to words and sentences.

All of these four motor abilities are essentially complete at 18 months and are completed then only through almost constant practice in all four fields throughout the baby's waking hours: *balance,* by rolling, turning, attempting to sit, pulling up and standing; *reciprocation* in the legs, by kicking, crawling, walking; *reach and grasp,* by the constant playing with toys, sucking the hands, putting objects in the mouth, standing supported; and *speech,* by crying, screaming, experimenting

with sounds produced by tongue and lip motions, imitation of others, and finally words and sentences. In the absence of the child's ability to carry out one or all of these fundamental activities, it can be seen that it would be impossible to approximate, with prescribed exercise, the amount of motor activity he would normally accomplish.

The second motor developmental period represents an entirely different mechanical problem. It is the growth period from 18 months of age to 11 years. During this period growth occurs sometimes evenly, but more often in spurts. In the normal child the speed of growth of the bones and that of the muscles and tendons is essentially even. In the presence of motor handicaps, however, there is frequently a discrepancy, so that if the bones grow longer and the muscles and tendons do not, there will be gradually increasing deformities developing, which do not of themselves indicate a progressive disease but only a progressive growth imbalance.

This imbalance will frequently block the normal advances in all motor fields, excepting speech, and bring about abnormal motor functions. Growth discrepancies are frequently obvious in large joints, such as the knees, but occur with equal frequency in small joints, such as the fingers, where they may interfere progressively with manipulative activities. In the spine and rib muscles they produce insidious but eventually profound postural changes. This period, from 18 months to 11 years, is in a way a latent motor period. The fundamentals have been mastered and activity and play are essentially unskilled. In a previous study it has been shown statistically, in a large number of cases, that the average age at which skills can first be mastered is 11 years, and it has also been shown that postural corrective programs are relatively unsatisfactory as regards results under this age and of greatly increased value beyond this age. It is also at about 11 years that in both boys and girls the character of games shows a greater complexity as regards skill. Even the handwriting begins at this age to take on individual characteristics.

The third important motor developmental period begins therefore at 11 years and extends to about 18 years. This period seems completely independent of the onset of puberty. The skill development begins before puberty and is apparently not influenced appreciably by whether puberty is early or late. The real importance of this period of skill development is that cooperation and effort to improve or to overcome the handicap can be counted on, and the nature and types of treatment can be much more intricate. Methods of overcoming motor handicaps, dependent on cooperation, in younger children will seldom succeed and certainly results will only be obtained in a small number of cases. The motor training of young children must be so set up that skills or cooperation beyond their age will not be called upon.

The fourth motor period is the stabilized period, extending from 18 years of age on. Practically all skills and techniques have been learned and while perfection of motor action may progress still further, this will follow only specialized fields of endeavor. It is entirely possible to develop new skills after this age but usually the time is devoted to specialization and application to the fullest extent possible of those abilities already learned.

It therefore becomes apparent that the time of onset of a motor disability is of great significance, especially with regard to the motor clinical picture which results, but also in connection with the type of re-education indicated. Before these can be clearly evaluated it is necessary also to determine the substitutions which have occurred. It is impossible to deprive an individual of any specific motor ability without expecting a different type of motor activity to take its place. In the case of the legs, when walking is prevented, rolling or crawling may be overdeveloped and the use of walkers which support the weight and eliminate the necessity for learned balance may seem to the child so satisfactory as to prevent

him from further efforts at free walking. In arm handicaps, where the legs are essentially normal, there may be a substitution of the legs for the arms, and they are used for turning pages and moving toys so well that the arms become more and more neglected. In the speech field it has been found that the usual compensation is sign language. There is, however, nearly always a great increase in general motor activity. The mentally normal speechless child is always overactive both in walking and in the types and intricacies of arm use. This frequently overflows into the behavior field, and temper tantrums, biting, head banging, and similar behavior are seen. This should not be mistaken for mental deficiency, a priori, as in many instances the establishment of speech will of itself cause a complete return to normal behavior.

Therefore, it can be seen that if all of the motor deprivations are studied carefully and the results of these deprivations evaluated, a very clear picture of the child can be evolved. It is necessary in all cases of motor handicap to determine first how much motor development took place before the onset of the handicap. In certain instances, hyoscine hydrobromide, for example, has proved very effective in relieving the motor handicap in postencephalitic dystonia. The age at which the encephalitis occurred is very important, since the drug can only at best restore abilities which had been already learned. The drug is notoriously ineffective in children with cerebral palsy existing since birth, and its effectiveness increases with the age of onset, whether the cerebral palsy resulted from injury to the brain or from disease such as encephalitis.

Developmental retardation will, of course, be found to occur in most instances, especially in handicaps present since birth. The child who cannot walk or who has little or no use of the hands misses a great deal of experience with his immediate environment. The absence of speech eliminates most of what is learned by conversation and answers to questions. When the handicaps are multiple, that is, when legs and arms, or legs and speech, or arms and speech are handicapped, the retardation which results is more than double that found in the case of a single handicap.

The effect on maturity of a neuro-orthopedic handicap is very complex. It is best first to make an evaluation of the child's developmental ages. Beginning with a chronologic age of 12 years, for example, a Binet mental age might show 8 years. A study of the skeletal system by x-ray might indicate a bone growth age of 13. The glandular development might suggest 11, and the skill age, 6. The social maturity test might be 5 years. As a result of these age discrepancies, it might be determined that the emotional age approximated 4 years. It would not be assumed that these age determinations were correct, but by investigating the age at onset of the handicap and extent of involvement it could be found why the tests resulted as they did. Mental age tests and social age tests presuppose a normal motor system for their accuracy, and it is essential that all factors due to the handicap and its resultant limitations be considered.

It is impossible to develop walking, unless the fundamental reciprocation of the legs has been learned. Speech cannot be expected until the child has gone through the amount of preliminary practice of the normal baby. Skills and more complicated techniques depend on a thorough knowledge of these fundamentals and the evaluation of the growth factors of childhood.

In conclusion, it may be said that there are four motor developmental periods: (1) birth to 18 months, when the fundamentals are learned; (2) 18 months to 11 years, which is a latent period and physical growth is responsible for changes; (3) 11 years to 18 years, when skills are learned; and (4) 18 years on when perfection of previously learned motor patterns takes place.

The age of onset of a handicap is very important in a determination of its clinical picture and effects on the individual.

Treatment is largely dependent on knowing the age of onset and evaluation from this of the type of treatment advisable.

CHAIRMAN GESELL.—Dr. Phelps' reference to these different ages reminds me of a Boston boy who was asked, "How old are you, young man?" He looked like a young man; he had horn-rimmed spectacles, which he removed and wiped reflectively as he said, "My osseous age is 11; my social age is 8; my intellectual age is 16, but I cannot, sir, tell you what is my chronological age. Is it not negligible?"

In developmental diagnosis chronologic age is not negligible. We are obliged to express maturity in terms of age.

Dr. Phelps, you mentioned the fact that the age of onset of a handicap is important in the determination of its clinical picture and its effect on the individual and, therefore, on the prognosis. Would you also say that there are individual differences with respect to the reserves of the nervous system, the vitality of the nervous system, in addition to the age factor? Would you also admit, perhaps, that there may be a nutritional factor such as Dr. Holt referred to, which in turn affects the outlook in the prognosis?

DR. PHELPS.—I should think there is no question about that. The whole developmental picture is so complex that it is probably impossible for any one of us to think of all the factors that come into it. I am sure that the nutritional factors would very much influence the motor skill and I imagine Dr. Holt would agree that some of the vitamin B difficulties would disturb the nervous system enough to interfere with skills.

DR. AMATRUDA.—You spoke of the retardation which disability causes by interfering with performance. Do you not think that retardation is often more apparent than real because a disability incurred early interferes more with the acquisition of a skill than with the performance of the skill?

DR. PHELPS.—This was demonstrated in the film that Dr. Amatruda showed to illustrate the case of the child who prefers to continue feeling objects rather than grasping them. That was obviously due to the fact that the child's sense of touch was not impaired at all, whereas the child's ability to grasp was very much impaired. Therefore, that child would establish a great interest in tactile sensations. If the child was not forced to grasp in any way, the child's tactile ability would be something like that of the blind man who feels with his hands, whereas the grasping ability would have a lesser development because the child would find it difficult and uninteresting.

That is why I think it is true that these retardations in some cases may be real in the sense that the child will neglect the difficult thing and overemphasize the easy thing, so that the developmental picture will be very much out of proportion in different lines.

DR. AMATRUDA.—My point was that a great many of these children were sent to me as defective children because they were failing to grasp and to sit and nearly all of them learned to grasp very well later on. This was really an exaggeration of their handicap because of their extreme youth.

DR. PHELPS.—I like to draw a fairly sharp line between retardation and defectiveness. We have to have two such words. Certainly the retarded child means to me a very different child from a defective child.

DR. ALDRICH.—It would seem valuable to me if Dr. Amatruda and Dr. Phelps would get into a huddle and take a case report and see how they differentiate between those apparent defects and the real ones.

DR. AMATRUDA.—One of the most important differentiations is, of course, the establishment of appropriate substitutions. If a child is simply failing to show any sign of a function, if the child is not interested in the object you give him, it is a little discouraging. If, however, he does develop a substitution which shows some resemblance to the normal pattern, if he reaches with his head instead of his arms, at least we know that reaching is potentially there. If he touches and twiddles instead of grasping, he is at least exploiting, and that gives us the hope to go on with the expectation that we can develop the function, that we can increase the child's interest and get him over the hurdle of working against his handicap. He must be encouraged to do that rather than accept the substitution.

DR. PHELPS.—That can be further exemplified in the speech field, where you can measure a child's potential mental ability by the degree and success of his sign language substitution. If the child has good use of his arms and has made no sign language to substitute for lack of speech, then the picture looks rather bad. Some of these children develop such a complicated and such a perfect sign language that they can make every person who comes in contact with them understand exactly what they want.

CHAIRMAN GESELL.—We now pass to an important practical problem. The physician may appreciate the significance of the developmental point of view but how can he get the parents to think in developmental terms? He must become a teacher. In the person of Dr. Aldrich we have this combination of a wise pediatrician and teacher. He will tell us how to get over to the parents a developmental outlook and developmental philosophy.

## How to Get Parents to Think in Developmental Terms

C. Anderson Aldrich, M.D., Chicago

I feel very apologetic before you this morning because what I have to offer is only the sort of thing that you have all been doing, I think, for many years. But it seems important to me that we review our ideas about how we can get parents thinking in developmental terms because it has so much to do with the baby's competency. The parents should be the first people interested in such a matter.

We, as pediatricians who know natural developmental progress, have learned to expect that normal children will "act their age." This might be called the pediatrician's approach to mental health. It is a philosophically tolerant attitude and it is scientifically sound.

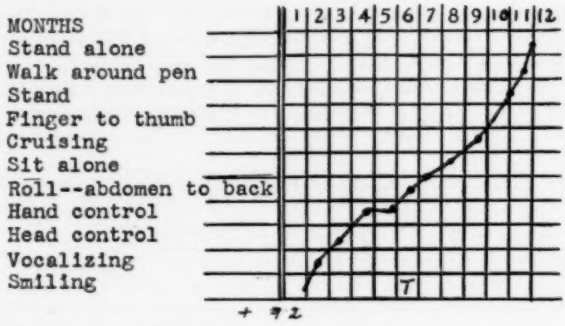
But no matter how advantageous this may be to us, it will not exert its most favorable effect on the child's health unless it can be thoroughly implanted in the minds of his parents. If, for instance, we merely minimize the importance of some "childish mistake" in behavior and tell a parent that it is of little moment, we are not living up to our possibilities in helping the child over this rough spot. In addition, it is desirable to point out that such behavior is *normal* for that age rather than that it is an excusable slip. Ideals must be scaled down to the realities of development.

Since I have for many years been interested in the problem of how to make parents conscious of the stereotyped progress of growth and have worked up a technique which I thought helpful, perhaps outlining it to you will be the best way to open a discussion of the subject.

Before delivery, if possible, or during the post-partum period otherwise, explain that the mother did not make and never will make her child. He has grown before and he will grow after birth, according to the hereditary laws of his species,

race, and family. Point out that parents, nurses, and doctors provide the environment for this growth exactly as a gardener fertilizes and waters his plants. Make the point that the more they know about the type of growth of this particular species, the better they will be able to provide for the proper cultivation of the soil and provide the things which help the organism to develop.

After the first conference, during the period in the hospital, you get an opportunity to demonstrate the newly born status of the baby. This can be described accurately and demonstrated. I often take a baby's clothes off in the mother's room and show her the reactions which the newborn baby has so as to bring out the point that at that time he is acting on a reflex, highly emotional, brainless, primitive, compulsive basis.




After that I think one has the best opportunity to teach developmental progress by using the child as a demonstration point at the monthly conferences with mothers. You can demonstrate each time the baby comes in what he is going to do next month. He will do what you said he was going to do, because that is the way babies grow, unless there is something pathologic about the child.

After having demonstrated during the first year that the baby will do a predictable new act before you see him the next time, you put across the idea that there is a regular sequence of growth, that the parents are not teaching the baby everything he learns, and that he leads an independent existence in life even from the beginning.

I am going to throw on the screen a graph, with most abject apologies to Dr. Gesell, as it is a very lazy graph. I might even call it a lazy pediatrician's graph, because it requires no impedimenta to make the estimate of progress at each month in the first year of life. It has been useful to me in the office in charting very grossly the baby's progress. The various accomplishments shown in this graph will be a month or two ahead of Dr. Gesell's developmental schedule. That is not because the babies born in Chicago are any speedier than the babies born in New Haven. It is merely that I took the mother's word for the time an act was first accomplished. In Dr. Gesell's figures I think he has taken the final perfection of each act. This makes my schedule a little ahead of his.

(Slide shown. See accompanying graph.)

You see here the accomplishments of the child during the first year. You make a cross when the baby first *smiles*. Sometimes you can observe it. Usually the mother observes it. The point to bring out to the mother is that this is the baby's first demonstrable voluntary act and that socializing is beginning in the child's life through his own efforts.

The next development is his *vocalizing*. That also comes out from within, and it is a very good idea to explain to the mother at this time that the baby is try-

ing hard to learn to talk. Thus the mother can see from her own observation how the baby tries to repeat syllables. Talking also comes from within.

The next is the attainment of *head control.* From the standpoint of parent education it seems to me it is a good point to make, that at this time the child is showing his curiosity. We must remember that children lie on their backs before this period and see nothing but the ceiling and that which comes down to them from the ceiling. When they can raise the head up and crane around they get to be able to see around the floor and view the place where things come from. In this stage the child is demonstrating his inquisitive nature.

The next step is *hand control,* when the child can reach out and get hold of a rattle. This leads to voluntary arm and hand movements which introduce the child to play and work, which will occupy his waking hours during the rest of his life. It is well to point out that play is a child's way of working. It is his most dignified occupation.

The next step demonstrates his ability to roll over from the back to the front, which comes at about 5 or 6 months. That is the child's first demonstration of his desire to go places. This effort eventually leads to the crawl and walk, which we will speak of later.

The next development is his *sitting up,* which comes along between his rolling over and his crawling, as a rule. This is his first ability in assuming the upright posture and it helps him considerably in feeding situations.

Following that he begins to *crawl* or cruise about. I was going to ask Dr. Gesell later on to explain why, when everything else is so rigid in development, babies have so many different ways of cruising about. I have never been able to understand that. They need our help in giving them opportunities to perform this act. That is why a play pen is ordinarily employed.

At about this time, or soon after, babies are able to put the finger and thumb together, which makes them good handlers of objects. I think someone has remarked that that is the most important accomplishment of man since it makes him able to fashion weapons to kill his enemies. It will probably kill us all off before we are through with it, but still it may be our greatest accomplishment. No other animals have this ability to the degree that man has.

Then finally comes his proudest achievement, *standing upright* in his pen, getting up on his feet. Soon after that he *walks about his pen with support.* Then he achieves *standing alone* and finally *walks alone.* It is useful to point out to mothers that the time the baby can actually step out and walk may depend not so much upon his ability to do this as upon his courage or lack of it.

It seems to me that in spite of many discouragements one can actually demonstrate to parents an all-important lesson with this technique. If they learn the inevitableness of each step in growth they will come to feel that they are not personally responsible for each advance. Development becomes a part of their consciousness and they come to realize that future development also will go on in much the same way. Thus they can be assisted in meeting on a developmental basis the problems which will come up later in childhood. The same sort of processes will continue to work, gradually leading the child through progressive immature patterns to the final adult status. Dr. Montgomery has aptly called this the development of usefulness.

This attitude should immeasurably assist us in such problems as will inevitably arise later on. Obedience will become of minor importance as compared to self-discipline. Reading, writing, and arithmetic will be matters which can be learned only after the child has reached a stage of maturity at which he can learn those three arts. His handedness, right or left, will be respected because it will be realized that he will do best with the hand he would naturally use. Masturbation

will appear as a part of normal sexual maturity, and adolescence will appear as a period of gradual maturation, in which children grow up, mate and marry, and finally have their own children, thereby relegating to the status of old folks.

DISCUSSION

DR. AMATRUDA.—I think Dr. Aldrich's point of view is particularly valuable in the field of guidance. If the parents have been brought up to the developmental viewpoint, problems of management can be handled sanely. I always cite to parents the similarity between the acquisition of walking, of obedience, and of toilet control, for example. "Falling down" is as much to be expected in one function as in another. It is easy for the parents to acquire tolerance and understanding if they have the proper point of view.

DR. ALDRICH.—I have been told by many people who are supposed to know better than I that you cannot teach parents because they are spoiled and grown up. I feel emphatically that you can teach parents if you will demonstrate these things to them, and it is the sort of conditioning that has a very friendly sort of connotation.

CHAIRMAN GESELL.—I think there is no doubt, Dr. Aldrich, that parents respond very spontaneously to the developmental approach itself because it releases so many tensions and because they see that there is a certain relativity about things, which gets them away from an overmoralistic point of view which biology certainly is modifying.

DR. ALDRICH.—Dr. Holt, how early do you feel it is advantageous to add solid foods, cereal, and vegetables to infants' diets?

DR. HOLT.—It would be hard to find two pediatricians in agreement on that point. It seems to me that the extreme points of view are to be avoided. I am not one of those who advocate their use at one month nor am I one of the conservatives who wait until nine or ten months. It is our practice in Baltimore to start solids at about the fifth month. It seems to me that no hard and fast rule should be laid down. It is possible to upset a baby's digestion by the unwise use of solids but this should not occur if one exercises a certain amount of intelligence.

QUESTION.—Dr. Holt, do you agree with Dr. Jolliffe that there are no suitable methods of determining mild deficiencies of the B factors in infants?

DR. HOLT.—I believe we have methods for assaying deficiencies of thiamin, as well as riboflavin and nicotinic acid deficiencies, which are practicable as hospital procedures. These require the use of a fluophotometer which costs roughly $300.00 at present; it can be operated by a technician of moderate intelligence.

QUESTION.—If there is a retention of thiamin in diarrhea, did I understand you to say that there is occasional need for additional vitamins in disease? How does this illustration of retention show a need?

DR. HOLT.—If the stores of thiamin are adequate, the administration of thiamin will cause a relatively large amount to spill out in the urine. When the body is in need of thiamin, more thiamin is retained. Does that answer the question?

QUESTION.—Does Dr. Holt approve the use of four or five vitamin preparations such as Vi-penta, Hepi, Multicebrin, and so forth?

DR. HOLT.—Since we do not know all the factors of the B complex, it seems wiser to employ foods such as liver, yeast, and wheat germ and concentrates made from them which presumably contain all the factors, using the pure vitamins only as supplements in the case of specific or suspicious symptoms.

CHAIRMAN GESELL.—Before Dr. Aldrich became the discoverer of the old-fashioned truth that babies are human beings, he wrote a little book on children's appetites. So I will direct this question to him.

In cultivating good appetite, why not encourage early finger feeding, even at 5 months, when the child is getting the pleasure and satisfaction of putting things into his mouth?

DR. ALDRICH.—I wish Dr. Davis were here to answer that question and back her methods. She showed in a very humorous way how quickly children do learn to feed themselves by various methods: finger, palm, and fist methods. They rapidly learn to eat without spilling any on the floor. Of course, the use of man-made implements in feeding delays for a considerable time the child's efficiency in feeding himself. I think it is a perfectly logical thing to allow them to use their own methods and after a while, we may get radical enough to let babies feed themselves as soon as they are able.

CHAIRMAN GESELL.—Before Dr. Aldrich lays down the microphone would he speak to Dr. Holt's point about the inadequacy of breast milk?

DR. ALDRICH.—I agree thoroughly with the idea of Dr. Holt that very likely there may be serious deficiencies in the prenatal nourishment of the baby and also deficiencies in the breast milk. Many years ago I made a very superficial sort of a study of the diets of the mothers of sick young babies at the Children's Memorial Hospital. Those diets, pediatrically speaking, were grossly deficient, and theoretically, at least, could not provide the unborn child with adequate nourishment. I felt that we could not expect to make good babies out of poppy seed rolls and coffee.

I think Dr. Holt's position that breast milk is deficient in many instances is perfectly well taken and I go a long way with him. But I think we should not carry over this idea to mean that we should stop breast feeding. Whether or not breast milk contains all the vitamins, babies ought to be breast fed and we can add the vitamins in some other way. I do not think Dr. Holt meant you to feel that he advised taking babies off the breast for that reason.

DR. HOLT.—I would like to make my own position clear. I was not criticizing breast feeding, for I believe in it. Nor was I insisting on breast milk. I merely advocated supplementing it.

QUESTION.—Dr. Phelps, please repeat the name of the drug that is of value in postencephalitic syndromes, also the approximate dosage and method of administration.

DR. PHELPS.—I was merely taking that as an example. I am not a neurologist by profession, but I do know there has been a great deal of work done with hyoscine hydrobromide and various drugs which are related to that.

I believe the best work on that is probably the work of Dr. Leslie Holman, but I cannot give you the reference to it. It points out that the usual dosage of hyoscine hydrobromide by mouth, which is $\frac{1}{200}$ gr., is so small that it is not particularly effective in the postencephalitic syndrome, and that the dosage must be stepped up quite high in some instances to produce relief of some of the Parkinsonian symptoms. I believe in some instances the dose has been brought up as high as $\frac{1}{50}$ or $\frac{1}{25}$ gr. three times a day, but only by very gradual stepping up and watching for adverse symptoms. I have seen some of these results myself, and in some instances they are very remarkable.

QUESTION.—Dr. Phelps, what is the optimal time to start active physiotherapy in spastics? Is it best to accentuate training in the performances they do best?

DR. PHELPS.—I think the best time to start training is as early as you can possibly get the child. Methods of training can be developed which can be almost reflex in their nature and not dependent in any way on the cooperation of the child. There are many little pantomime exercises to which the child can be conditioned by rhymes and by other rhythmic sounds. The earlier these can be started the sooner bad habit formations will be eradicated.

Would you read the rest of the question?

QUESTION.—Is it best to accentuate training in the performances they do best?

DR. PHELPS.—I think that would bring the child out of focus in a way in that the thing the child does best would be very much pushed ahead and the thing that the child does worst would be allowed to slip back. As a matter of keeping up the child's interest it is necessary to put some emphasis on the thing he does best but the others should receive a great deal of attention.

QUESTION.—Dr. Phelps, if skills are not developed until after the age of 11 years, then why start children in piano or violin or dancing before this age?

DR. PHELPS.—I have often wondered about that. I started violin lessons at the age of 6, but in looking back it does not seem to me that I made any progress in skill before 11. I did learn the fundamentals, so that when the time came to play difficult music, the mechanism was there. But I do not think that skills develop very much before 11. It is important, however, to train the child in the fundamental use of the fingers and so forth earlier than 11 years. The onset of real skill will be seen then. That is apparent in handwriting.

CHAIRMAN GESELL.—I think we ought to welcome all contributions from the floor.

QUESTION.—In the light of what is known concerning the development of a baby's nervous system, would you discuss the proper age at which so-called "toilet training" should be begun.

CHAIRMAN GESELL.—I will ask Dr. Amatruda to say something about that.

DR. AMATRUDA.—We feel that the child shows he is ready when he begins to have long intervals between urination. When he is urinating every fifteen or twenty minutes, a great deal of time can be wasted in rushing him to the toilet and trying to keep him dry. When he begins to keep dry for an hour or longer, training can be begun. Perhaps the most reliable sign is when he begins to wake up dry from his nap. This is a developmental process and we take our cue from the child.

A lot of successful "training" (so-called) can be done before that time. Many small infants can be conditioned to use chairs and so on, but that is not really training. The mother watches the child and "catches" the child, as she often puts it, and she is really acting for him. Actually the child has to be retrained at the age when he begins to show a long span, usually at about 13 to 15 months.

QUESTION.—Dr. Holt, should vitamin A be given immediately in large doses to the newborn infant who is deprived of breast feeding?

DR. HOLT.—I think "immediately" is a very sudden time to give it. I would say it would be advisable to give it before two weeks have elapsed; preferably one week. We have seen vitamin A deficiency develop within a month in premature babies who have been fed on partial skim milk mixtures.

CHAIRMAN GESELL.—Here is a question that perhaps Dr. Phelps would want to answer.

QUESTION.—Where is the lesion in the child who used its feet so well?

DR. PHELPS.—I do not know exactly where the lesion was. A similar child showed a definite athetosis of the arms and of the neck. When I first saw her she was tossing a ball up to the ceiling of her crib and catching it with her feet. She could not walk. She had no use of her arms at all. They were in constant athetotic activity. I suggested putting shoes on the child right away because with such good ability in the legs I could not see why the child did not walk. In about six months the child did walk. From that time on she began to develop better use of the arms.

### Developmental Diagnosis and Clinical Pediatrics

CHAIRMAN GESELL.—This exhausts the questions from the floor. I shall say only a few words by way of conclusion.

In the light of the discussion this morning it seems clear that pediatrics is bound to enlarge steadily the scope of its clinical protection of infants and young children. Who could possibly take over the developmental problems and solve them apart from medical diagnosis and medical supervision? We cannot conceive a separate and independent mental hygiene service when it is realized that the first three years of life are almost entirely under the care and oversight of the pediatrician, as child specialist and as general practitioner.

His position in the whole scheme of medicine is unique, and it is strategic. He cannot use his authority to the full unless he brings his clinical skill to bear on problems of development, with the same purposiveness with which he diagnoses disease. Accurate diagnosis is the most fundamental requirement. Mental hygiene measures and child guidance efforts are pointless and even harmful if they do not rest upon sound diagnosis. In fact the primary responsibility of the physician is to make a considered diagnosis and then to interpret the implications of that diagnosis constructively to the parent. This looks like a truism, but it is worth mention because under the pressure of parents and social workers there is a real danger that even the hard-headed pediatrician will embark upon mental hygiene and guidance programs which put the cart before the horse because they are not supported by adequate diagnosis. Diagnosis remains the essential work horse.

The practicing pediatrician has three functions: diagnosis, therapy, and supervision, and the greatest of these is diagnosis.

No one can predict the shape which the clinical diagnosis and supervision of child development will assume in the future. It is probable that with the return of peace, there will be a much greater mobilization of the resources of positive medicine to safeguard the growth of the human infant. The safeguards will be more comprehensive; they will be clinical; they will be individualized. They will be applied to all types of children, normal as well as the defective and deviant.

The recent report of the Committee in Graduate Medical Education has recognized this trend, as have various committees of the Academy. The certification board has done its part to keep the clinical aspects of growth and development to the fore.

Medical schools, however, have not managed to give the integrated problems of child development adequate definition and interpretation. We do not need a new discipline in the medical curriculum, but we do need a reorientation of teaching which will bring the total embryology of the postnatal child into the focus of diagnosis and of understanding. The most fundamental function of an infant is development. We must get the medical student to think clinically in terms of development. We need to recruit more young men and women and train them for leadership in this field which has an inevitable future.

# News and Notes

Dr. Richard A. Bolt, of the Cleveland Child Health Association, led a seminar group on "Providing for Healthful Living of the Preschool Child" at the recent meeting of the National Association for Nursery Education in Detroit. Outgrowth of the conference was the creation of a planning commission to direct attention to the importance of considering the well-being of young children in all defense planning. Mrs. Rose Alschuler of Chicago, author and staff member of Winnetka schools, will head the commission.

Dr. Allan M. Butler of Boston, Mass., has been made Medical Regional Director of Region I (New England) for the Committee on National Defense.

Dr. Louise Taylor Jones, formerly of Washington, D. C., died recently at McLean, Va.

The eighth Pan-American Congress on the Child will be held in Washington, D. C., May 2-9, 1942, instead of March 28–April 4, 1942. The session will be divided into three sections: Prevention of Diseases of Children and Medical Care, Education and Recreation, and Social Aspects of Protection of Children and Economical Help Through the Family.

# Book Reviews

**The Blood Bank and the Technique and Therapeutics of Transfusion.** Robert A. Kilduffe, M.D., and Michael DeBakey, M.D., St. Louis, 1942, The C. V. Mosby Co., pp. 558. Price $7.50.

This is not only an important but also a most timely monograph. There has been a steadily increasing use of blood and plasma for therapeutic purposes in recent years with constant changes and improvements in techniques. The formation of hospital blood banks has been rapidly extended. The opening in recent months of blood donor services by the American Red Cross to obtain sera for war medical purpose has led to a tremendous general interest in the subject, and "blood" is well on the way to displacing "vitamins" as the popular subject of lay medical conversation. It can be conservatively stated that over one-half million of our citizens will become "donors" during the present calendar year. Thousands of questions are being asked daily in regard to this highly technical subject and this monograph contains all the answers.

Leaving aside this element of timeliness, the monograph is a most valuable contribution to medical literature. It is complete, thorough, well written, and splendidly illustrated, and it is obvious that both authors are unusually well qualified to write the text. After an interesting historical introductory chapter, there is a thorough

discussion of the rationale, indications, and contraindications for transfusion. This is followed by a discussion of the use of blood with chapters on the blood bank, its operation and typing and the changes occurring in stored blood. Following this, three chapters are given to a discussion of plasma, its use and preparation, and the preservation of citrated and dried plasma. In the last two chapters, about a third of the volume, the methods, techniques, and complications of transfusion are discussed. Each chapter is followed by an extensive bibliography. There are, for example, 913 references to the literature cited following the chapter on the indications and contraindications for transfusion. One of the most valuable features of the book is the thoroughness with which the technical processes discussed have been illustrated, some 214 in all, with a color plate on blood typing reactions. Both the authors and publishers are to be congratulated on producing such an excellent book on a subject of such timely importance.

**The Hearing of School Children.** Monograph of the Society for Research in Child Development, Antonio Ciocco and Carrol E. Palmer, Washington, D. C., 1941, National Research Council.

A study of 14,000 school children in Washington, D. C. The authors conclude that the phonograph audiometer in common use for testing the hearing of school children is not entirely satisfactory as conditions other than auditory may affect the results. In a study of the children with defective hearing, the authors stress the importance of infection of the nasopharynx in childhood. Tonsillectomy had not been of value in preventing auditory impairment. The monograph is of particular value to physicians interested in school medical service.

**Social Influences Affecting the Behavior of Young Children.** Monograph of the Society for Research in Child Development, Ruth P. Koshuk, Washington, D. C., 1941, National Research Council.

A critical review of the many studies that have been made of the relationship of social influences upon human behavior, with a bibliography of over 500 references. Presents in an unbiased way the many conflicting views on the role of social influences.